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Article

Functionality of innovative and generic celluloses in metronidazole formulations

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The wide variety of excipients available calls for evaluation of their functionality, in this case of the pharmaceutical performance of microcrystalline celluloses and sodium cross-linked carboxymethylcelluloses from different sources. This evaluation includes parameters such as powder flow, compactibility, ejection pressure and dissolution from fast-release tablets as well as from floating granules and controlled-release tablets. In a previous study, the excipient Carmacel® presented better disintegration properties compared to Croscarmellose®. However, the evaluation showed better compactibility performance for Croscarmellose®. These characteristics were observed using pure excipients. Nevertheless, these advantages have not been confirmed in tests employing immediate-release or modified-release formulations containing metronidazole. Regarding microcrystalline celluloses, the present comparative evaluation between pure Alfacel ® types 101 and 102 and pure Avicel® types 101 and 102 showed better compactibility performance for the latter. However, for metronidazole formulations, this advantage was not evident in the innovative excipient. Notwithstanding, this study revealed better compactibility performance of microcrystalline cellulose type 101. In terms of powder flow properties, Avicel® and Alfacel® showed similar performance. However, the results revealed better powder flow employing microcrystalline cellulose type 102 for both excipients. Based on the results obtained, it can be concluded that the employment of innovative and generic excipients have both advantages and disadvantages. The observed differences however, tend to disappear as the excipients are diluted in a formulation, thereby equalizing their influence on product performance.

Uniterms: Excipients/functionality. Microcrystalline celluloses. Sodium cross-linked carboxymethylcelluloses. Croscarmellose. Carmacel. Avicel. Alfacel. Tablets/disintegrants. Pharmaceutical dosage/forms**.**

A variedade de excipientes disponível no mercado requer adequada seleção desses no que se refere à sua funcionalidade, como no caso de celuloses microcristalinas (Avicel® 101 e 102 e Alfacel® 101 e 102) e de carboximetilceluloses de sódio reticuladas (Croscarmellose® e Carmacel®), provenientes de diferentes fontes. Assim sendo, o desempenho farmacotécnico desses excipientes deve ser avaliado quanto ao fluxo e característica de compactação do pó, à pressão de expulsão do núcleo, ao perfil de dissolução de comprimidos de liberação imediata e modificada assim como de grânulos flutuantes. Em um trabalho anterior, o excipiente Carmacel® apresentou melhores propriedades de desintegração quando comparado ao Croscarmellose®, porém, no que se refere à característica de compactação a avaliação revelou melhor desempenho para o Croscarmellose®. Tais características foram observadas empregando apenas os excipientes. Porém, tais vantagens não foram confirmadas nos ensaios empregando as formulações de liberação imediata ou de liberação modificada contendo metronidazol. No que se refere às celuloses microcristalinas, a avaliação comparativa entre Alfacel® puro dos tipos 101 e 102 e Avicel® puro dos tipos 101 e 102 revelou melhor desempenho desse último quanto à característica de compactação, no entanto, para as formulações contendo metronidazol não foi possível demonstrar tal vantagem para o excipiente inovador. Porém, o estudo revelou melhor desempenho quanto à característica de compactação da celulose microcristalina do tipo 101. Quanto às propriedades relativas ao fluxo de pó, o Avicel® e o Alfacel® apresentaram desempenho semelhante. Porém, o estudo revelou melhor fluxo de pó no emprego

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da celulose microcristalina do tipo 102, para ambos os excipientes. Considerando os resultados obtidos, pode-se concluir que o emprego dos excipientes inovador e genérico apresentam vantagens e desvantagens. No entanto, as diferenças observadas tendem a desaparecer em função da diluição desses na formulação, equalizando, dessa forma, sua influência no desempenho do produto.

Unitermos: Excipientes/funcionalidade. Celuloses microcristalinas. Carboximetilceluloses de sódio reticuladas. Croscarmellose. Carmacel. Avicel. Alfacel. Tabletes/desintegrantes. Dosagem farmacêutica/formas.

INTRODUCTION

The formulation process require a clearly defined product profile along with information on the physical and chemical properties of the active ingredient, of the most common excipients, and on the operation principles of the manufacturing equipment available for commercial production. The active pharmaceutical ingredient (API) properties of dose, solubility, compactibility etc., are the major constraint on formulation, and define how the active ingredient will respond to the stresses of the manufacturing process and to its ultimate use by the patient. Once the API properties are fully understood, the excipients and the process pathway can be carefully selected to overcome any apparent deficiencies in the API properties. This leverages the unique functionality of each excipient and the benefits of each manufacturing unit operation (Hancock, 2009).

The characterization of pharmaceutical excipients using a materials science approach has helped design drug formulations to obtain a desired set of performance properties. For tablets, a better understanding of the compression properties of a drug, alone and in combination with other potential components, facilitates the development of better formulations and products. The mechanical properties of a material play an important role in powder flow and compaction properties by influencing particle-particle interaction and cohesion, while reliable mechanical property information can be useful in (a) choosing a processing method, (b) selecting excipients with properties that will mask the poor properties of the drug, and (c) helping to document what went wrong. Despite the complexity of the mechanics of pharmaceutical systems, mechanical property measurements constitute the most systemic, rational approach to formulation design (Skinner, 1998).

The excipients are included in the formulation because they possess properties that, in conjunction with processing, allow the medicine to be manufactured to meet the required specification. These desirable excipient properties relate to its functional performance or functionality. Functionality has been defined as: a *desirable property of an excipient that aids manufacturing and improves the manufacture, quality or performance of the drug product.* The reality is that functionality can only be properly assessed in the context of the finished pharmaceutical product, and each formulation will have its own particular requirements for functionality (Moreton, 2009).

Because functionality is linked inextricably to the formulation and process, and all formulations are different, establishing a widely accepted standard for a particular excipient's functionality proves problematic. One formulation's functionality can be another formulation's dysfunctionality (Moreton, 2004). However, surrogate functionality tests can be considered for use as a general reference.

In a previous study, the surrogate functionality of different microcrystalline celluloses and sodium cross-linked carboxymethyl celluloses was investigated. The surrogate functionality properties used were particle morphology and particle size distribution, compactibility, ejection pressure and the disintegration properties of pure excipients and their compressed tablets. The innovative celluloses Avicel and Croscarmellose showed advantages over the generic celluloses Alfacel and Carmacel. Avicel PH 101 and 102 showed an average of 26 % greater compactibility than both types of Alfacel, while the compactibility of Croscarmellose was greater than that of Carmacel by about 50%. Avicel tablets compacted at a compaction pressure of 47 MPa exhibited shorter disintegration times (3.7 min) than Alfacel tablets (28 min), while Carmacel showed better disintegrant properties than Croscarmellose. This occurred despite similar particle morphology, size and size distribution. As expected for hygroscopic and insoluble materials, all celluloses showed low ejection pressures and no significant difference could be established among the different celluloses (Díaz, Villafuerte, 2010).

Excipients can be categorized by the function performed in a formulation. However, many excipients have multiple functions. For example, microcrystalline cellulose can function as a diluent, a binder and a disintegrant. Tablet excipients are grouped into different functionalities, one approach includes the following five functionalities: adsorbents, binders/diluents, disintegrants, glidents, and lubricants (McCarty, 2003).

Metronidazole, a 5-nitroimidazole with bactericidal activity against most anaerobic and facultative anaerobic

bacteria and protozoa, is widely used for the treatment of anaerobic bacterial and protozoal infections. The drug has few adverse reactions, most commonly nausea, dry mouth, vomiting, and diarrhea. Neurologic toxicity is rare and has included peripheral neuropathy, headache, dizziness, syncope, vertigo, and confusion (Patel *et al*., 2008).

Metronidazole has been used as a model drug for floating tablets with a probable gastric retention, because of a general assent about the benefits of eradication of *H. pylori* in patients with peptic ulcer. Drugs administered systemically are absorbed into the blood stream and distributed throughout the host patient via the circulatory system, which can result in bacterial resistance. When administered locally, this limits the adverse effects of systemic administration and there is a higher concentration of medication reaching the target site (Lara-Hernández *et al*., 2009). Metronidazole has been used also for local eradication of Helicobacter pylori in the form of floating beads (Javadzadeh *et al*., 2009).

Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process, while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation (Tanwar, 2006).

Recently, many studies have reported solid dispersions using Gelucires (polyglycolized glycerides) by fusion and solvent evaporation techniques. Gelucire-39/01 is a lipophilic carrier which is frequently used for this purpose; the suffixes 39 and 01 refer to its melting point and its HLB, respectively. Gelucires belong to a family of materials made up of glycerides and fatty acid esters of polyethylene glycols. Gelucires are available with a range of properties depending on their hydrophilic lipophilic balance (HLB). They have a HLB over a range of 1 to 18, and a melting point between 33 °C and 70 °C (Shrivastava *et al*., 2009; Patel *et al.*, 2007a).

Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparations of sustained release formulations. Gelucire 43/01 has been used for the design of multi-unit floating systems of a highly water-soluble drug, diltiazem HCl. The granules were retained in the stomach for at least 6 hours. Approximately 65% to 80% drug was released over 6 hours with initial fast release from the surface (Shimpi *et al*., 2004).

The aim of this study was to assess the functionality of Avicel, Alfacel, Croscarmellose and Carmacel P (CC) in metronidazole fast-release formulations containing different microcrystalline celluloses and cross-linked sodium carboxymethylcelluloses. Additionally, the study sought to assess the functionality of the cross-linked sodium carboxymethylcelluloses in controlled-release floating formulations containing metronidazole and Gelucire 39/01.

MATERIALS AND METHODS

Materials

The materials used in this study were microcrystalline cellulose, Avicel PH 101, batch P107818846 and PH 102, batch: P206816698, FMC Biopolymer; microcrystalline cellulose, Alfacel type PH 101, batch 12, and type PH 102, batch 13, Reliance Cellulose Products Limited; cross-linked carboxymethylcellulose sodium, Croscarmellose sodium, batch T0801C, FMC Biopolymer; cross-linked carboxymethylcellulose sodium, Carmacel P(CC), batch 02, Reliance Cellulose Products Limited; metronidazole, batch: 03121402, Química Alkano; Gelucire 39/01, batch: 5E0907-2 Y GE2007-2, Lubrizol; Stearic acid, batch: 31503361, Helm de México.

Metronidazole tablets

Table I shows the formulations employed to obtain metronidazole fast-release tablets, using Croscarmellose and Carmacel as disintegrants and Avicel PH 101 and 102 as diluents, as well as Alfacel types 101 and 102.

TABLE I - Metronidazole formulations containing different microcrystalline celluloses and cross-linked sodium carboxymethylcelluloses

Components (%)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
Metronidazole	50	50	50	50	50	50	50	50
Alfacel PH 101	-----	-----	47	47	-----	-----	-----	-----
Alfacel PH 102	-----	-----	-----	-----	-----	-----	47	47
Avicel PH 101	47	47	-----	-----	-----	-----	-----	-----
Avicel PH 102	-----	-----	-----	-----	47	47	-----	-----
Stearic acid	1	1	1	1	1	1	1	1
Croscarmellose	-----	2	2	-----	-----	2	-----	2
Carmacel P-(CC)	2	-----	-----	2	2	-----	2	-----

The materials corresponding to each formula were sieved (sieve number 20) prior to being mixed. The drug and 30% of the diluent were mixed with a spatula in a mortar for 15 min. After addition of the rest of the diluent plus the disintegrant, the powders were mixed for a further 15

min. Finally, the previous mixture was mixed for 15 min with the lubricant. The tablets were flat, with a diameter of 12.8 mm and a total tablet weight of 500 mg, equivalent to a metronidazole content of 250 mg. The powders were compacted for 10 seconds in hydraulic presses adapted in our laboratory with a manometer measuring up to 50 MPa and 105 MPa, accurate to ± 2% and ± 1% respectively, and similar to the Carver standard manual presses (Carver Inc., 2010).

Metronidazole controlled-release floating formulations

Table II shows the formulations used to obtain metronidazole/Gelucire controlled-release floating granules and tablets, using Croscarmellose and Carmacel as disintegrants. Floating granules containing metronidazole were prepared using the melt granulation technique. The drug:lipid ratio used to prepare the different formulations was 50:40. To study the effect of the disintegrants Croscarmellose and Carmacel at different proportions were added separately to the formulations. The proportions of disintegrants were 5, 10 and 15 parts. Lipid was melted at 50°C, and the drug and disintegrants mixture was added, mixed well, and cooled to room temperature. The mass was passed through a number 20 sieve to obtain uniform-sized granules.

TABLE II - Metronidazole formulations containing Gelucire 39/01 and different proportions of sodium cross-linked carboxymethylcellulose

Components (parts)	G05	G06	G07	G08	G09	G10
Metronidazole	50	50	50	50	50	50
Gelucire 39/01	40	40	40	40	40	40
Croscarmellose	10	5	15	0	0	0
Carmacel P-(CC)	0	0	0	10	5	15

The tablets were flat with a diameter of 12.8 mm and a weight equivalent to 500 mg metronidazole per tablet. The powders were compacted for 10 seconds in hydraulic presses adapted in our laboratory with a manometer measuring up to 50 MPa and 105 MPa, accurate to ± 2% and ± 1% respectively, and similar to the Carver standard manual presses (Carver Inc., 2010).

Powder flow

The equipment used for this test was adapted in our laboratory and similar to that used to determine the tap density of powders (Kibbe, 2000). The tapper was set to a rate of 74 taps per minute and adjusted to elevate the graduated cylinder up to a height of 18 mm. This device uses a 100-mL graduated cylinder joined to a glass funnel with an orifice of 20 mm that can be closed with a glass rod. Once the sample is weighed and placed in the closed funnel, the device is started while removing the glass rod at the same time. The time required for the 30 g of powder to empty from the funnel through the funnel orifice, is used to calculate the speed of the powder flow. The registered results were the average of 10 repetitions on the same sample without further treatment.

Compactibility and ejection pressure

Corresponding quantities of the powder blends were compressed for 10 s at different compaction pressures in a hydraulic press. The tablet crushing strength was measured in triplicate, registering the results as an average. For this purpose, hydraulic presses adapted in our laboratory were used with a manometer measuring up to 1.1 MPa and 4.1 MPa, accurate to ± 1 and 2%, respectively, similar to the Carver standard manual presses (Carver Inc., 2010) with a pointer for the maximal pressure reached. The procedure entailed placing each tablet diametrically between two flat surfaces and applying pressure until the tablet broke. The maximal pressure reached was taken as the tablet crushing strength. In the same way, the necessary pressure to eject the formed tablets was taken as the ejection pressure. For this purpose, the pressure was applied on a punch while the die was supported on an acrylic cylinder, allowing the tablet release from the die where it was formed.

Dissolution of metronidazole

Dissolution studies were performed in 900 ml of HCl 0.1N using the paddle method (USP 26), at 50 rpm and 37 ºC (JT R09, TEMSA, Mexico). The amount of metronidazole released over time was determined by withdrawing samples at various time intervals. The concentration of metronidazole was obtained by measuring the absorbance at 276 nm in a Beckman DU-650 ultraviolet spectrophotometer. This procedure was used to evaluate all the metronidazole formulations, including immediate-release tablets, floating granules and controlled-release tablets. The results for each time point of three different dissolution curves are registered as an average in the figures. These average values were used to calculate the regression parameters of each dissolution curve representing a given formula.

RESULTS AND DISCUSSION

Powder flow

Flow characteristics of the pharmaceutical excipients are of major concern with respect to the handling and compaction of the powder materials, especially for directly compressible excipients. Blend flow is important to ensure bulk blend transfer into the tablet press hopper and consistent die fill. Variation or difficulty in the bulk flow or die fill can contribute to tablet weight variations.

Figure 1 shows the powder flow through an orifice of 20 mm of different metronidazole formulations. As can be seen, formulations with microcrystalline cellulose type 102 exhibited better powder flow, with an average of 16.7 g/s, followed by formulations with microcrystalline cellulose type 101 with an average of 9.2 g/s. This is attributed to the greater average particle size of the type 102 formulation. Avicel PH 102 showed better fluidity because of its more granular form and larger particle size (Ahjel, Lupuliasa, 2008). Although the average powder flow of the raw materials Alfacel (23.8 g/s) and Avicel (29.1 g/s) differs by about 20%, the differences between formulations containing Alfacel and Avicel are smaller and without a trend favoring one vendor or the other. Formulations containing Avicel 102, average powder flow of 16.1 g/s, exhibit a something slower powder flow, compared to Alfacel 102, average powder flow of 17.4 g/s, while Avicel 101 formulations (average powder flow of 12.0 g/s) show a faster powder flow than those formulations with Alfacel 101 (average powder flow of 6.4 g/s).

The use of different disintegrants had no effect on the powder flow. Formulations containing Carmacel showed an average powder flow of 13.0 g/s (average of the four formulations: 13.7, 13.7, 6.4 and 18.2 g/s) while those containing Croscarmellose showed an average powder flow of 12.9 (average of the four formulations: 10.3, 18.5, 6.4 and 16.6 g/s). The excipients dilution in the metronidazole formulations mask the better flowability of Croscarmellose (2.3 g/s) over that of Carmacel (1.1 g/s), determined with the pure excipients and a funnel with an opening of 15 mm.

The results of powder flow of metronidazole formulations containing celluloses of the type 101 (Avicel – 12 g/s, Alfacel – 6.4 g/s) were consistent with surrogate functionality tests performed previously using a funnel with an opening of 15 mm, showing a faster powder flow for pure Avicel PH 101 (2 g/s), compared to that of pure Alfacel type 101 (0.7 g/s). However, this is not the case for type 102 celluloses which exhibit similar powder flow in metronidazole formulations (16.1 – 17.4 g/s) while the surrogate functionality

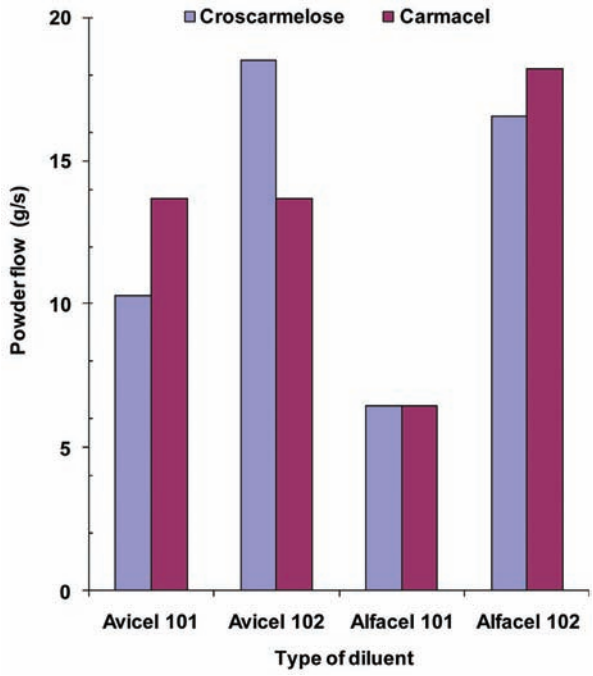

FIGURE 1 - Comparative powder flow, through a glass funnel with an opening of 20 mm, of formulations containing different type and vendor microcrystalline cellulose as diluent and Croscarmellose and Carmacel as disintegrant.

tests, done earlier using a funnel with an opening of 15 mm, clearly show better flow for Avicel 102 (5 g/s) compared to Alfacel 102 (0.7 g/s). It is worth mentioning that despite the greater particle size of Alfacel type 102, the powder flow determined with an opening of 15 mm was similar to that of Alfacel type 101. In the same way, it is notable that the drug influences the behavior of the different formulations but this was beyond the scope of this study and so its effect was considered constant.

The initial greater flowability of the innovative Croscarmellose, Avicel PH 101 and Avicel PH 102 over the generic Carmacel, Alfacel 101 and Alfacel 102, was only confirmed in metronidazole formulations for Avicel PH 101. The greater flowability of Avicel 102 and Croscarmellose over that of Alfacel 102 and Carmacel vanished after dilution in metronidazole formulations.

Compactibility

The compactibility, defined as the ability of materials to form agglomerates after compression, was described with equation 1 (Castillo, Villafuerte, 1995a; Castillo, Villafuerte, 1995b).

$$\ln(-\ln(1-\frac{D}{Dmax})) = n * \ln Pc + I \qquad (1)$$

Where: *D* denotes the tablet's hardness, *Dmax* the maximal tablet hardness obtained, *Pc* the compaction pressure, *n* the slope of the curve, and *I* the intercept of the curve.

The compactibility curves obtained depict the relationship between the hardness or crushing strength of the tablets and the compaction pressure used to obtain them. Figure 2 shows the experimental data and the calculated compactibility curves of formulations designed as F 1, F 4, F 5 and F 6, obtained by regression of experimental data. These formulations contain Alfacel and Avicel types 101 and 102 as a diluent and Carmacel as disintegrant. The lineal regression was obtained from the data adjusted according to equation 1. As can be seen, the data is described properly with the applied model. Table III summarizes the regression parameters obtained for all different formulations.

Figure 3 shows the calculated tablet crushing strength (compaction pressure of 23.9 MPa) for all different formulations. Results clearly show greater compactibility of formulations containing microcrystalline cellulose type 101 (average tablet crushing strength of 166 kPa) over those containing type 102 (average tablet crushing strength of 144 kPa), mirroring previous observations (Ahjel, Lupuliasa, 2008). These data confirm the higher compactibility of microcrystalline cellulose type 101 (average *Dmax* = 843 kPa) over that of the type 102 (average *Dmax* = 821 kPa) observed with surrogate tests (Díaz, Villafuerte, 2010).

A less significant difference in compactibility can be observed between the sodium cross-linked carboxymethyl celluloses from different vendors, innovator and generic. Formulations containing Croscarmellose displayed an average crushing strength of 159 kPa while formulations containing Carmacel showed an average of 151 kPa. This confirms the higher compactibility of Croscarmellose over

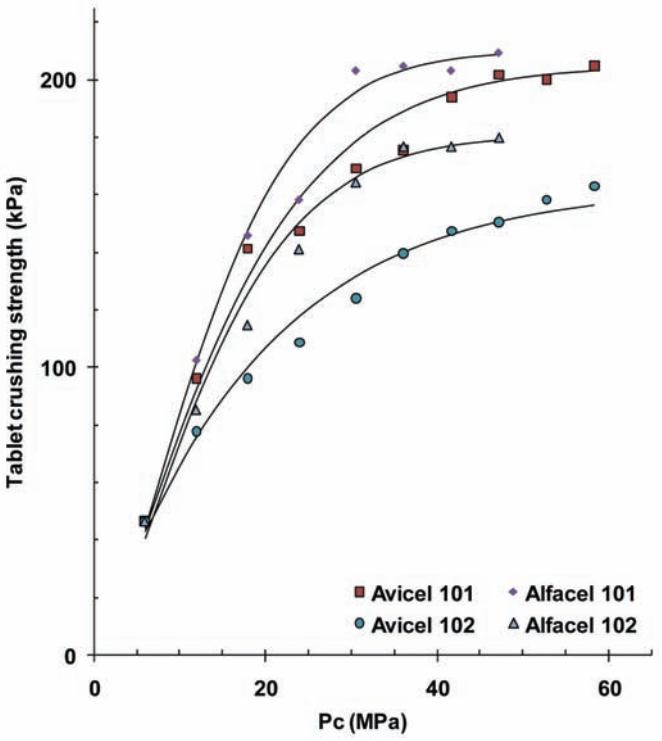

FIGURE 2 - Compactibility curves of metronidazole formulations containing stearic acid, Carmacel and different diluents. Tablets weighed 500 mg and had a diameter of 12.8 mm.

that of Carmacel, determined with the pure excipients, although in metronidazole formulations, a much smaller difference was seen compared to pure excipients.

Contrasting the compactibilities of microcrystalline celluloses from different vendors, reveals that formulations containing Alfacel display greater compactibility or crushing strength (169 kPa) when compacted at 23.9 MPa, than formulations containing Avicel (141 kPa). These results are in contrast with those obtained for pure ex-

TABLE III - Regression parameters of compactibility curves (Eq. 1) of metronidazole tablets obtained with formulations including different types and vendors of microcrystalline cellulose and cross-linked carboxymethylcellulose

Formulation	Tablet crushing strength Pc=41.7 MPa (kPa)	Slope	Intercept	r^2
F 1 - Avicel PH 101- Carmacel	196	1.312	-12.831	0.960
F 2 - Avicel PH 101- Croscarmellose	184	1.078	-10.499	0.776
F 3 - Alfacel PH 101- Croscarmellose	201	1.331	-12.748	0.915
F 4 - Alfacel PH 101-Carmacel	207	1.491	14.407	0.972
F 5 - Avicel PH 102-Carmacel	146	1.033	-10.171	0.978
F 6 - Avicel PH 102- Croscarmellose	154	1.251	-11.943	0.815
F 7 - Alfacel PH 102-Carmacel	177	1.403	-13.571	0.981
F 8 - Alfacel PH 102-Croscarmellose	193	1.588	-15.159	0.846

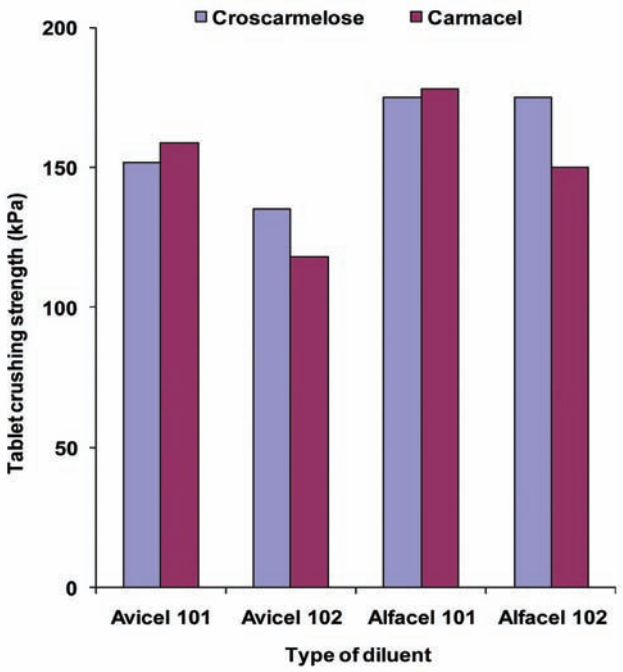

FIGURE 3 - Comparative calculated tablet crushing strength attained at a compaction pressure of 23.9 MPa in formulations containing different types of microcrystalline cellulose as diluent, and two different types of cross-linked carboxymethylcellulose as disintegrant.

cipients, where Avicel showed a greater compactibility.

In a previous study, the innovative Avicel and Croscarmellose showed superior compactibility over the generic celluloses Alfacel and Carmacel, assessed with the pure excipients. Avicel PH 101 and 102 showed an average 26 % greater compactibility than the average for both types of Alfacel, while the compactibility of Croscarmellose was greater than that of Carmacel by about 50% (Díaz, Villafuerte, 2010).

It seems that Croscarmellose contributes to a greater extent than Carmacel to the attained tablet crushing strength in metronidazole formulations containing these disintegrants, although the difference in compactibility is currently only 5% versus the initial 50%. On the other hand, the observed greater compactibility of Avicel over that of Alfacel of about 26% assessed with the pure excipients, vanished in metronidazole formulations. Metronidazole formulations containing Alfacel display greater average compactibility (169 kPa) than those formulations containing Avicel (141 kPa). The initial compactibility advantage of Avicel (about +26%) became a disadvantage (about -20%) in metronidazole formulations.

Although the superior compactibility of Croscarmellose over that of Carmacel assessed with pure excipients can be confirmed in metronidazole formulations, the difference in compactibility of formulations containing these disintegrants is smaller than that initially estimated with pure excipients. The initially greater average compactibility of Avicel (26%) over that of Alfacel could not be confirmed in metronidazole formulations. Formulations containing both types of Alfacel displayed greater compactibility than those containing Avicel.

Ejection pressure of the tablets

The force necessary to eject a tablet involves the distinctive peak force required to initiate ejection by breaking the diewall tablet adhesion. The second stage involves the force required to push the tablet up the die wall, and the last force is required for ejection of a tablet from the die (Patel *et al*., 2007b).

Figure 4 shows, as an example, curves of ejection pressure against compaction pressure of metronidazole tablets containing Croscarmellose as disintegrant, and Alfacel 101 and 102 as diluent.

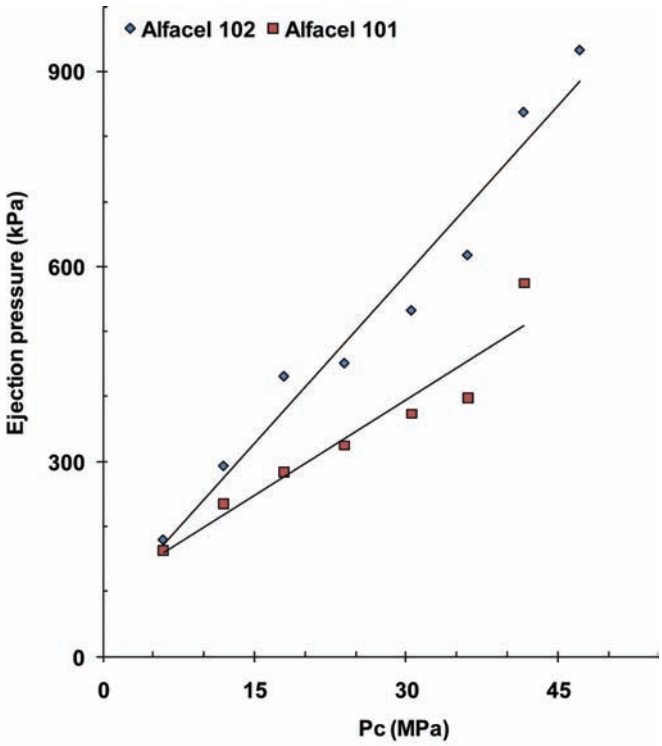

FIGURE 4 - Curves of ejection pressure for formulations containing different diluents, Alfacel type 101 (F3) and 102 (F8), and Croscarmellose as disintegrant.

Figure 5 shows the comparative ejection pressure of all the different formulations at a compaction pressure of 23.9 MPa, calculated after regression of curves similar to that of Figure 4. These show that the ejection pressure

profiles of formulations containing different disintegrants show no significant differences. The ejection pressure profiles depicted in Figure 4 show the extreme differences between the formulations, and both of them are sufficiently small to enable fluid production process. These results evidence the low ejection pressures that are characteristic of materials derived from cellulose while no relevant difference was observed between formulations containing different disintegrants and different diluents. The good lubricant properties of microcrystalline cellulose mask any possible differences due to dissimilar vendors.

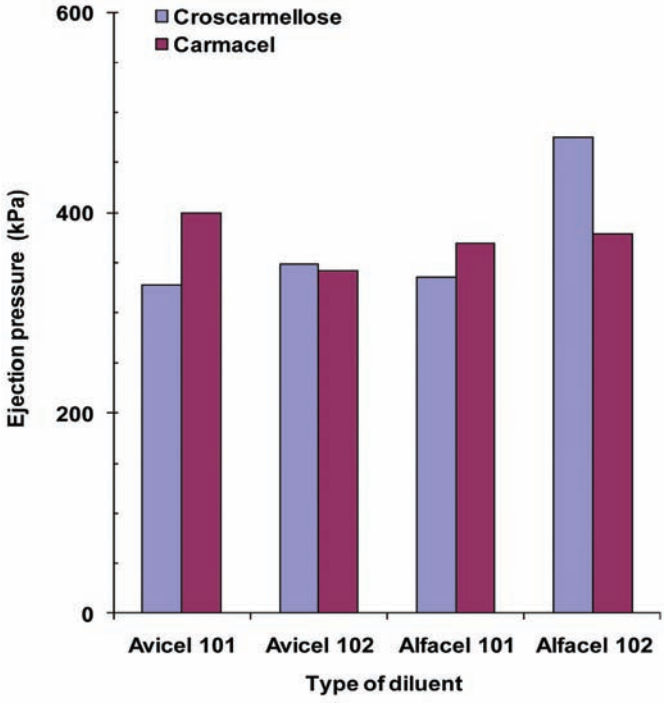

FIGURE 5 - Comparative calculated ejection pressure (Pc=23.9 MPa) of formulations containing different type and vendor microcrystalline cellulose as diluent and Croscarmellose and Carmacel as disintegrant.

DISSOLUTION OF METRONIDAZOLE

The dissolution of metronidazole fast-release formulations was too fast to allow the observation of any differences among the formulations. Tablets compacted at 6 MPa dissolve almost 100% of the drug after 5 minutes. The same occurred with tablets compacted at 47 MPa, dissolving almost the total quantity of the drug after 5 min. This type of tablet, with water soluble drugs, display the same good dissolution results regardless of the type or vendor of microcrystalline cellulose (101 or 102) and sodium cross-linked carboxymethyl cellulose used.

In order to disclose any differences as disintegrant or dissolution facilitating agents of sodium cross-linked carboxymethyl celluloses from different vendor, the release rate of metronidazole formulations was slowed down using Gelucire 39/01. Table 2 shows the different metronidazole formulations containing Gelucire, as a dissolution restricting agent, and Croscarmellose and Carmacel as disintegrants or dissolution facilitating agents. The dissolution behaviour was the only determined characteristic of these formulations and was determined in granules as well as tablets obtained with these granules, compacted at 47 MPa.

Figure 6 shows the dissolution profiles of metronidazole (50 parts) floating granules containing Gelucire 39/01 (40 parts) and different proportions of Croscarmellose and Carmacel (5, 10 and 15 parts). The dissolution profiles, although different for different disintegrants, do not show a tendency indicating better functionality of any one of the disintegrants. Using formulations containing 5 parts of the disintegrants, Carmacel formulations exhibited a higher dissolution rate over Croscarmellose formulations. However, upon using 10 parts of the disintegrant instead of 5 parts, the opposite occurred. The use of 15 parts of the disintegrant showed overlapping dissolution profiles for formulations containing both disintegrants.

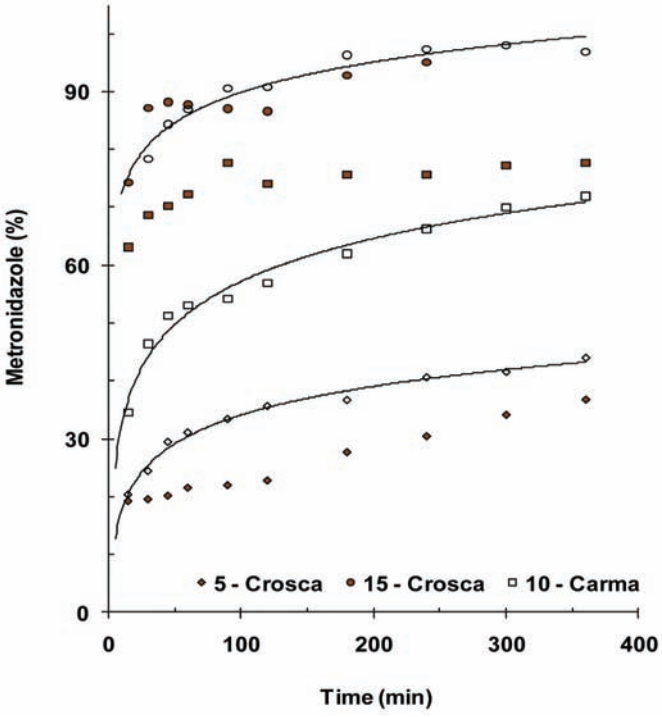

FIGURE 6 - Dissolution of metronidazole (50 parts) granules containing Gelucire 39/01 (40 parts) and different proportions of Croscarmellose (Crosca) or Carmacel P (CC) (Carma) (5, 10 and 15 parts).

The better tablet disintegrating properties showed by pure Carmacel over pure Croscarmellose disappears in metronidazole floating granules formulations. Metronidazole floating granules containing Carmacel did not dissolve faster than granules containing Croscarmellose, as could be expected because of the better disintegrating properties showed by Carmacel in tablets of the pure excipients.

Increases in disintegrant proportion were accompanied by increases in drug dissolution, with a tendency to attain a limit not corresponding with the total drug content but apparently corresponding with the ability of the lipidic Gelucire to conceal the drug from the dissolution medium. An explanation for these results is that increasing proportions of the disintegrant dilutes or decreases the possibility to cover the drug with Gelucire, allowing a greater quantity of metronidazole to interact directly with the dissolution medium. However, it is also possible that increasing proportions of the swelling disintegrant open up the Gelucire structure to a greater extent, forming channels that facilitate drug dissolution. The channelling increases with greater proportions of Carmacel and Croscarmellose. This means that Croscarmellose and Carmacel behave in the same manner and have the same power to facilitate the dissolution from the floating granules.

Whatever the case may be, a part of the drug that remains completely covered with the lipophilic Gelucire could not be dissolved. Increasing proportions of the disintegrants make a greater proportion of the drug accessible to the dissolution medium. In this way, greater proportions of the disintegrants allow a greater plateau of drug dissolution to be attained, independently of the disintegrant used.

Figure 7 shows the dissolution profiles of metronidazole tablets obtained with the floating granules. In this case, Croscarmellose displays a greater functionality as an agent favouring drug dissolution, functionality that decreases at low disintegrant proportions. Croscarmellose formulations exhibit greater release rates at proportions of 10 and 15 parts of the disintegrant. However, at low disintegrant proportions (5 parts) metronidazole tablets containing Croscarmellose or Carmacel display overlapping drug dissolution profiles. Unlike the granules, the tablets do not float. The non-floating tablets release the drug in a more gradual manner. The dissolved drug increased continuously with time throughout the 6 hours of the dissolution test.

Generally, the use of Gelucire slowed down the release rate of metronidazole. From dissolution rates allowing almost total drug dissolution in less than 5 minutes, Gelucire granules allow a metronidazole dissolution ranging

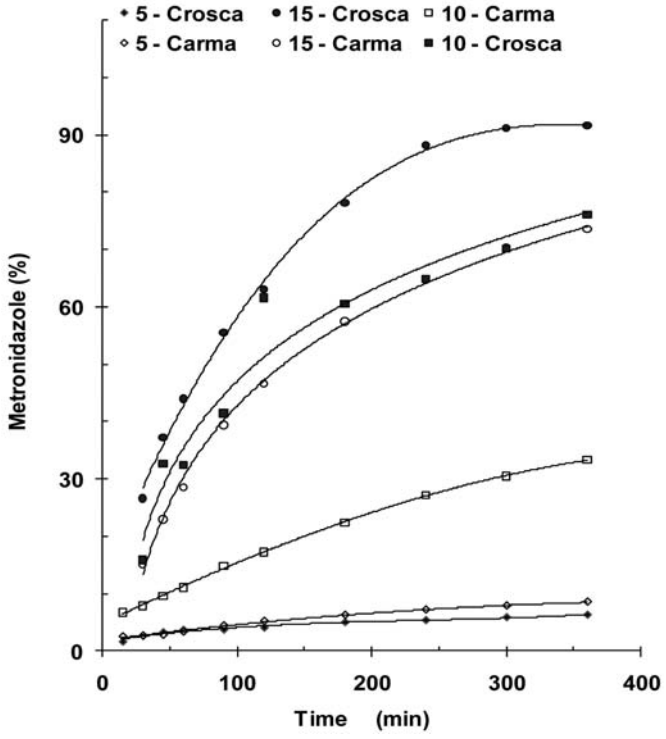

FIGURE 7 - Metronidazole (50 parts) dissolution from tablets containing Gelucire 39/01 (40 parts) and different proportions (5, 10 and 15 parts) of Croscarmellose (Crosca) or Carmacel P (CC) (Carma), obtained at Pc=47 MPa.

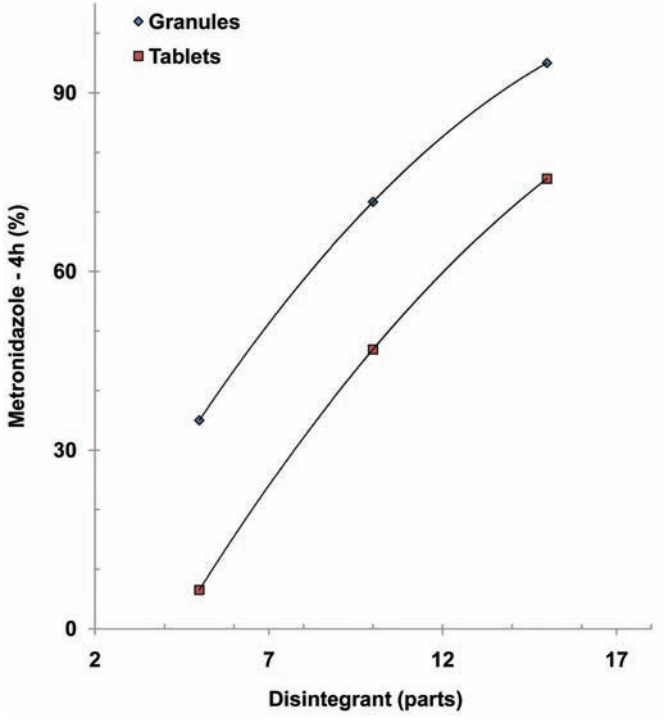

FIGURE 8 - Effect of disintegrant proportion (5, 10 and 15 parts) on average metronidazole (50 parts) dissolution after 4 hours, from granules and tablets containing Gelucire 39/01 (40 parts) and Croscarmellose or Carmacel P (CC).

from an average of 38% to almost total drug dissolution (98%) after 4 hours, while the tablets allowed the drug dissolution in a range from 7.5% to 95% after the same 4-hr period. In both cases the tendency shows increasing drug dissolution at higher disintegrant proportions. This behavior can be seen in Figure 8. Although the drug dissolution was sufficiently slowed down with the tablets, it is necessary to review their deficit in floatability.

CONCLUSION

The conclusion of this work has to be addressed in two parts, first a conclusion about the predictability of an excipient behavior in a given formulation through the knowledge of surrogate functionality test, and secondly a conclusion about the functionality of excipients from different sources or vendors, innovative and generic excipients.

Although the surrogate tests do not precisely reflect the excipients' behavior in a formulation they remain good indicators of their potential functioning, particularly when the excipients are used in higher proportions. It should to be taken in account that dilution of the excipients decreases their influence on the formulation performance and this means the predictability of their functioning becomes more uncertain.

The differences in performance of the excipients obtained from different vendors revealed that the generic sodium cross-linked carboxymethyl cellulose traded as Carmacel has the advantage over the innovative Croscarmellose of better disintegrating properties, while Croscarmellose exhibited greater compactibility than Carmacel, assessed with pure excipients. Nevertheless, these advantages could not be confirmed in fast-releasing metronidazole formulations, neither in the floating granules nor in the prolonged-release tablets. The higher compactibility of Avicel over Alfacel could not be confirmed with metronidazole fast-release formulations. None of the excipients displayed any advantage over the other in the compactibility of metronidazole formulations. However, greater compactibility of microcrystalline cellulose type 101 over that of type 102 was clear. On the other hand, both trade names of microcrystalline cellulose, Alfacel and Avicel, showed similar powder flow properties in metronidazole formulations. However, type 102 microcrystalline celluloses showed a higher powder flow compared to type 101 microcrystalline celluloses. The excipients dilution produces an equalization of their influence on the formulation performance.

As the excipients are increasingly diluted, the original differences obtained with the pure excipients or surrogate functionality tests have a tendency to disappear. Comparison of the innovative celluloses, Avicel and Croscarmellose, against the generic celluloses, Alfacel and Carmacel, show no definitive better performance of one over the other. The innovative celluloses showed some advantages and some disadvantages over the generics. In any event, the differences in performance tended to disappear as the excipients were diluted in the formulation, equalizing the excipients' influence on the formulation performance.

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