

Original Article

INFLUENCE OF FREE-FLOW EXCIPIENTS ON FUNCTIONAL PERFORMANCE OF NOVEONAA1 IN CONTROLLED-RELEASE TABLETS

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ABSTRACT

Objective: The aim of this work is the assessment of an eventual improvement in flowability of free flowing excipients on formulations containing Noveon AA1 and their influence on compactibility and release profile.

Methods: Mixtures containing 20% Noveon AA1 and variable proportions of metronidazole and the free flowing excipients Prosolv EasyTab and GalenIQ 720 and 721 were tested in their powder flow rate and the tablets compactibility and released profiles.

Results: The powder flowability obtained with GalenIQ is about 20% better than that obtained with EasyTab. However, it is lesser than that considered as acceptable for a high-speed tableting machine. EasyTab reduces the drug release up to a half along with a continuing flattening of the release profile. This is attributed to an increasing tortuosity of the drug release path as the proportion EasyTab increases. GalenIQ restricts drug release in about a third with a lesser change in the release mechanism. This is attributed to competition for the available water inside the tablet, between the hydrating Noveon AA1 and the dissolving GalenIQ. The compactibility of the metronidazole/Noveon AA1 mixtures increases after addition of EasyTab in about 3.5 N per unit percentage of the added excipient while GalenIQ does it in about 2.6 N.

Conclusion: The powder flowability of mixtures of metronidazole with Noveon AA1 was not suited for direct compression after addition of 40% of the free-flow excipient. The free-flow excipients reduce the metronidazole release rate and increase its compactibility. It was not observed a different clear functioning between both types of GalenIQ.

Keywords: Compactibility profiles, Powder flowability, Dissolution profiles, excipient functionality, Metronidazole, Controlled release, Noveon AA1, GalenIQ, EasyTab

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INTRODUCTION

Physical and technological characterization of drugs and pharmaceutical excipients is a requirement that provides data that can be predictive in nature regarding the performance of final dosage forms. Manufacturers generally provide some physical testing data, such as particle size, surface area, density or porosity [1]. Additionally, other technological tests may not be reported such as powder flowability, tabletability and performance in dissolution. These data provide insight into how a particular material will behave in a given process or final dosage form.

Noveon AA1 is an acrylic acid polymer with application to solid dosage formulations as a controlled release polymer. Noveon AA-1 has binding properties that provide helpful mechanical properties of tablet formulations, improved tablet hardness and decreased tablet friability. Nevertheless, its hygroscopicity demands processing with low relative humidity. It does not show a free-flowing behavior. Noveon AA1 has a very fine particle size and static loads. Further, segregation can occur in powder blend [2].

Noveon AA1 has been regarded as a matrix for controlled release, displaying enhancing properties of the overall controlled release performance of HPMC. Noveon AA1 also improves the compactibility, however, decreases the flowability [3]. Microcrystalline cellulose reduces the effect of Noveon AA1 to decrease the flowability of powder blends while dicalcium phosphate dihydrate increases importantly the flowability of blends containing Noveon AA1 [4].

The poor flowability is the main drawback that characterizes Noveon AA1. It displays a Carr's index (CI) or compressibility index of 39%, which stands for a cohesive or extremely cohesive powder [5]. Noveon AA1 is considered dysfunctional in this respect. Microcrystalline cellulose type 102 (CI=21.7%) is considered at the limit for powders that can be processed in a high-speed tableting

machine. The compressibility index of other excipients such as GalenIQ 720 (CI=13.8%), display values indicating a good powder flowability [6].

Direct compression is the simplest means of production of tablets dosage forms. It takes a blending of the drug with the appropriate excipients before the compression. Whereby the minimum number of excipients is mostly desired. Tablet development for oral delivery of drugs is accomplished by the availability and use of suitable excipients with multifunctionalities [7].

Aerosil is one of the most used compounds for flow regulation in pharmaceutical applications [8]. Aerosil has been employed to prevent obstruction of the flow of hygroscopic powders. Sennoside binary mixtures with microcrystalline cellulose showed an increased powder flow rate when added of 4% Aerosil [9]. The addition of Aerosil to mixtures of metronidazole with Noveon AA1 reduces the compressibility index; a proportion of 4% seems to be at the limit of improvement of powder flowability of that formulation [5].

Physical modification and/or co-processing of excipients have accomplished the purpose of direct compression excipients with the implementation of powder and tableting requirements. Various types of excipients involving physical modification and/or co-processing are currently in pharmaceutical applications. These products are commonly designed as free flowing excipients and maintain the powder velocity once it is in motion. These excipients show superior flow properties, mostly due to controlled particle form, particle size and particle size distribution.

GalenIQ 720 is a form of spherical agglomerated isomalt used for direct tableting and for filling capsules. Chemically, it is disaccharide alcohol in a 1:1 ratio of 6-O-D-glucopyranosyl-D-sorbitol and 1-O-D-glucopyranosyl-D-mannitol dihydrate (GSP/GMP). It is found in pharmacopeias as isomalt. Due to its properties as its taste and low-calorie content, as well as its low hygroscopicity offers advantages

over other polyols when formulated into pharmaceutical products. Particularly, it is used as an excipient in tablets [10-11].

A comparable product produced from a basic isomalt product with a GSP/GMP ratio of 3:1 is GalenIQ 721. The main difference between the two agglomerated products is their water solubility. Both agglomerated isomalt types with a mean particle size of about 240 μm have an excellent flowability, as reflected by a low Hausner ratio (1.14) and free flow through the smallest orifice (2.5 mm). Both agglomerated isomalt types display an improved lubricant sensitivity and good compaction properties [12].

GalenIQ 720 shows a particle size distribution with a $d_{50\%}$ of 200 μm that is 10% higher than that of GalenIQ 721 (180 μm). Its solubility (25 g/100 ml water) is lower than that of GalenIQ 721 (42 g/100 g water) [13].

The compactibility of GalenIQ 720 (134 N) is roughly 37% of that of microcrystalline cellulose (357 N). However, GalenIQ 720 exhibits an increased compactibility in mixtures with a lubricant, against the known fall of compactibility of microcrystalline cellulose [13-15].

The powder flow rate of GalenIQ 721 is approximately 63% larger than that of microcrystalline cellulose type 102 while its compactibility is about two-thirds lesser of that shown by similar tablets [16]. The excellent flow properties of GalenIQ 720 and 721 are attributed to favorable particle form and size distribution [17].

A co-processed excipient called Prosolv EasyTab acts as a binder, disintegrant, lubricant and a glidant. Its main recommended application is ready to use excipient composite. Prosolv EasyTab is a homogenous lubricant-coated high functionality excipient composite. It is composed of four individual components: a binder-filler (microcrystalline cellulose-96.50%), a glidant (colloidal silicon dioxide-2.00%), a super disintegrant (sodium starch glycolate-1.00%), and a lubricant (sodium stearyl fumarate-0.50%). These components maintain their chemical identities while synergistically providing increased functional performance [18-19]. The Prosolv EasyTab is particularly suitable for abrasive, bad flowing and fluffy actives formulations. This excipient composite shows an average particle size of 130 μm and an average bulk density of 0.36 g/ml [20].

A mixture of the drug Vardenafil hydrochloride with Prosolv EasyTab (5:97.5) showed a compressibility index of 14.6% and a tablet hardness of 5.2 kg/cm². These data stand for an efficient flow as well as compressibility properties [21].

The aim of this work is the assessment of an eventual improvement in flowability of free flowing excipients on formulations containing Noveon AA1 and their influence on compactibility and release profiles.

MATERIALS AND METHODS

Materials

The materials used in this study were Noveon AA1, obtained from Lubrizol; Prosolv EasyTab obtained from JRS Pharma; agglomerated isomalt (EP, BP, USP-NF), GalenIQ 720 and 721, from BENEOPalatininit GmbH, and metronidazole from Química Alkano SA de CV. All materials obtained from subsidiaries in Mexico. The drug and excipients were used as received.

Methods

Preparation of mixtures

Corresponding amounts of the materials were weighed to obtain 30 g of metronidazole mixtures with different proportions of each Free-flow excipient (Prosol EasyTab and GalenIQ 720 and 721): 5%, 10%, 15%, 20%, 30%, and 40%, maintaining a constant proportion of 20% for Noveon AA1 in all mixtures. The powders were transferred to a mortar and mixed manually for 30 min.

Assessment of the powder flow rate

A sample of approximately 25 g is weighed, and its flow rate assessed, through a glass funnel with an opening of 8 mm diameter. The funnel is placed on a graduated cylinder of 100 ml, which is mounted on a tapper. The sample is gently poured into the funnel,

whose bottom opening was blocked. While unlocked, the tapper starts the movement. The tapper is set at a constant speed of 60 taps per minute, tapping from a height of 1.5 cm. The time it takes to move the total powder poured through the funnel is registered. The flow rate is calculated by dividing the sample mass by the time. The assay is repeated five times, sieving the powder through a mesh number 20 after each measurement. The average of the five repetitions is taken as the flow rate.

Dissolution test

Tablets obtained as described in the subtitle compactibility and compacted at a compaction pressure of 109 MPa were used to determine the dissolution behavior. The dissolution profile was carried out for a period of six hours using a paddle apparatus at 50 rpm. Each time three tablets were placed in 900 ml of distilled water at 37°C. At predetermined time intervals, samples were removed, filtered and evaluated with a spectrophotometer (Beckman DU 650, $\lambda=319$ nm). After each sample was removed, the same quantity of liquid was replaced. The percentage of drug released was based on the total tablet content after dissolution in a magnetic stirring device.

Compactibility

Tablets weighing 150 mg were compacted for 10 s in a hydraulic press, at a series of compaction pressures from 27 MPa to 240 MPa, using 8 mm circular flat-shaped punch and die. Tablet crushing strength was measured in triplicate, registering the results as an average. For this purpose, a tablet hardness tester Erweka TBH30 was used. The procedure involved placing each tablet diametrically between two flat surfaces and applying pressure until the tablet breaks down.

RESULTS AND DISCUSSION

Influence of flow agents on the flowability of metronidazole/Noveon AA1 powder blends

In bulk powder applications, maintaining a free-flow behavior during processing is critical in order to minimize downtime and ensure product quality and homogeneity. A free-flow excipient possesses the ability to maintain the powder velocity once it is in motion. In this respect, multifunctional excipients such as EasyTab, GalenIQ 720 and GalenIQ 721 can serve as materials preventing packing of particles when mass is flowing. This type of excipient are considered to help ensuring free-flow of powdered formulations.

Fig. 1 depicts the effect of the above-mentioned excipients on the powder flow rate of metronidazole mixtures containing 20% Noveon AA1. The addition, of these different excipients, shows a better flowability of blends with GalenIQ compared to those blends with Prosolv EasyTab. Among the blends of the two different types of GalenIQ, there is no practical difference in their flowability. Although GalenIQ 720 displays a higher flowability at a high excipient proportion (equal parts of metronidazole and GalenIQ 720). GalenIQ is the excipient of choice with respect to flowability.

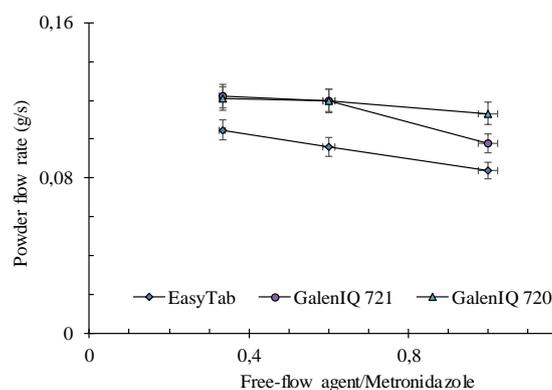


Fig. 1: Effect of different proportions of free-flow excipients/metronidazole on the powder flow rate of mixtures containing 20% Noveon AA1, n=5

The metronidazole used here displays a high flowability (6.2 g/s) when determined under the similar circumstances (orifice size and speed of the tapper). In the same way, GalenIQ 720 displays a similar flowability (5 g/s) [6]. On the other hand, Noveon AA1 exhibits a high compressibility index (39%) and quite a slow powder flow 0.0372 g/s. It indicates an exceedingly poor powder flowability [5]. The results obtained currently are in between of those of individual components of the blends. Although the powder flow rate of the blends containing GalenIQ is better than those of EasyTab, this powder flow is still about a half of the powder flow rate of microcrystalline cellulose type 102 [6].

Although a mixture of the Vardenafil hydrochloride with Prosolv EasyTab (5:97.5) showed an efficient flow, it occurred at a high proportion of the excipient [21]. Currently, excipient proportions of up to 40% does not show an adequate flow improvement. In the same way, the excellent flow properties of GalenIQ 720 and 721 [17] could not be confirmed when used here at proportions up to 40%.

Influence of flow agents on the release profile of metronidazole/Noveon AA1 tablets

Oral dosages with desired optimal release characteristics to meet the therapeutic windows usually either contain polymers in matrices or coated around multi particulates. The use of polymers such as Noveon AA1 displays drug release mechanisms where water molecules tend to diffuse into these systems, causing swelling which results in diffusion of drug molecules out through the swollen polymer matrix.

In this case, the kinetics of drug release was evaluated with the aid of a model based on the Weibull distribution (Eq. 1), which has been used for the evaluation of sigmoid release profiles from matrix systems. Mathematical models such as this one are normally used to investigate a proper "fit" for the experimental measurements of drug release. In this model, (% D) means the percentage drug dissolved at a time (t).

$$\ln\left(-\ln\left(1 - \frac{\% \text{ Dis}}{100}\right)\right) = \text{slope} * \ln(t) + \text{Intercept} \quad \text{Eq. 1}$$

Fig. 2 depicts the release profile of metronidazole from tablets containing 20% Noveon AA1 and different proportions of metronidazole and the free-flow excipient EasyTab. The experimental data were treated according to the above-mentioned model to obtain the depicted regression lines.

Table 1: Regression parameters of release profiles of metronidazole tablets containing different proportions of EasyTab and 20% Noveon AA1, calculated according to equation 1

| Easytab (%) | Slope | Intercept | r ² | t _{50%} (min) |
|-------------|--------|-----------|----------------|------------------------|
| 0 | 1.3447 | -6.743 | 0.997 | 115 |
| 5 | 1.4664 | -7.6508 | 0.989 | 143.7 |
| 10 | 1.5458 | -8.2589 | 0.985 | 164.9 |
| 15 | 1.2598 | -6.8335 | 0.996 | 169.6 |
| 20 | 1.2437 | -6.9679 | 0.993 | 201.9 |
| 30 | 1.3341 | -7.5454 | 0.981 | 217.2 |
| 40 | 1.3299 | -7.5554 | 0.989 | 222.6 |

Data calculated as a whole from three dissolution curves

Fig. 3 depicts the by regression calculated release profiles of metronidazole from tablets containing different proportions of EasyTab and a constant proportion of Noveon AA1 (20%). These curves were obtained from a calculated response surface. As above-mentioned, increasing proportions of EasyTab produce an increasing restriction of drug release. At the same time, the increasing proportions of EasyTab shift the release kinetics towards an order zero. The degree of curvature of the metronidazole dissolution profile decreases as the proportion of EasyTab increases, the release kinetics moving in the direction of a zero order kinetics.

In controlled release diclofenac sodium pellets, based on isomalt, sugar, and microcrystalline cellulose, it was comparatively observed that dissolution rates for the soluble sucrose-and isomalt-based

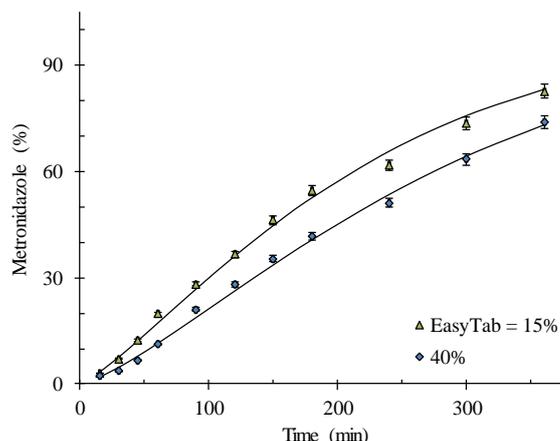


Fig. 2: Release profile of EasyTab/metronidazole tablets containing 15% and 40% EasyTab and 20% Noveon AA1, n=3. Experimental points and calculated regressions

Currently, the drug release kinetics does not correspond to a zero order. Even if the profile up to 3-4 h could be described itself as zero order. The metronidazole release profile is assigned to an anomalous transport including mechanisms of diffusion and relaxation of the polymeric matrix.

EasyTab obstructs metronidazole release. The higher obstruction corresponding to the higher EasyTab proportion. This behavior has been ascribed to the microcrystalline cellulose water insolubility that provides an additional barrier by increasing the tortuosity of the diffusion path, reducing the drug release rate. The microcrystalline cellulose content of EasyTab is 96.5% [22-23].

Table 1 summarizes the calculated regression parameters for the release profiles of metronidazole from tablets containing a fixed proportion of Noveon AA1 (20%) and varying proportions of metronidazole and EasyTab. As can be seen, an increasing proportion of EasyTab in the mixtures produces tablets with an increasing time to attain 50% drug dissolved. The use of increasing proportions of EasyTab increases the restriction degree of metronidazole release, prolonging the time necessary to dissolve 50% of the drug. The t_{50%} is in the range 115 min to 223 min, with a range width of 108 min.

pellets were similar and were significantly higher compared to those of the microcrystalline cellulose-based pellets [24].

Table 2 summarizes the calculated regression parameters for the release profile of metronidazole tablets containing a fixed proportion of Noveon AA1 (20%) and different proportions of GalenIQ 720. GalenIQ 720 also shows a restrictive effect on the release of metronidazole, although in a smaller range.

The effect of the GalenIQ 720 to restrict the release of metronidazole is lesser than that of EasyTab. The time for dissolving 50% of the drug (t_{50%}) is in a range from 115 min to 152 min, with a wide range of 37 min. This wide range is approximately 35% of that produced by tablets containing EasyTab.

Table 2: Regression parameters of release profiles of metronidazole tablets containing different proportions of GalenIQ 720 and a fixed proportion of Noveon AA1 (20%), Data calculated according to equation 1

| GalenIQ 720 (%) | Slope | Intercept | r ² | t _{50%} (min) |
|-----------------|-------|-----------|----------------|------------------------|
| 0 | 1.345 | -6.743 | 0.997 | 115 |
| 5 | 1.666 | -8.108 | 0.998 | 104 |
| 10 | 1.48 | -7.333 | 0.997 | 111 |
| 15 | 1.612 | -8.155 | 0.998 | 125 |
| 20 | 1.594 | -8.082 | 0.987 | 126 |
| 30 | 1.751 | -9.109 | 0.997 | 147 |
| 40 | 1.677 | -8.794 | 0.992 | 152 |

Data calculated as a whole from three dissolution curves

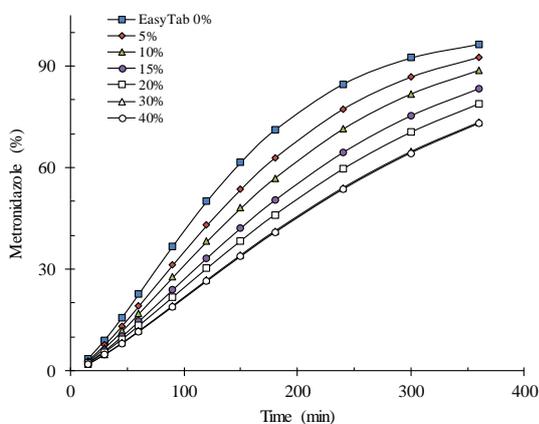


Fig. 3: Release profiles of metronidazole tablets containing different proportions of Easy tab and 20% Noveon AA1, obtained from a calculated response surface

The effect of GalenIQ 720 on the release profile cannot be ascribed to an obstruction effect or the addition of an extra barrier over the release path. GalenIQ 720 is water-soluble and must disappear after dissolution, leaving in the matrix an increased porosity and an increasing release rate. However, it does not happen. Instead, the effect of GalenIQ can be attributed to a delayed drug release. This delay occurred because of competition for available water inside the tablet. Both excipients, GalenIQ 720 and Noveon AA1 compete for the available water, delaying the polymer hydration and the GalenIQ 720 dissolution. The consequence is a decreased drug release rate. However, the lesser release rate is partially compensated by an increased matrix porosity after the dissolution of GalenIQ 720. The result is a reduced effect on release rate.

Competition for the available water inside a tablet has been observed in tablets containing a water-soluble diluent such as Pharmatose DCL11 and disintegrants with different hygroscopicity. Pharmatose DCL11 showed a less important improvement of norfloxacin dissolution when mixed with the high hygroscopic Starch 1500. The addition of Pharmatose DCL, 11 to tablets of the low hygroscopic PVP XL 10 and norfloxacin, showed no inhibition but potentiated the dissolution of norfloxacin substantially. These effects were attributed to competition for the available water inside

the tablet and to different water consume, for dissolution or hydration, by the diluent and the disintegrants [25].

Fig. 4 depicts the effect of GalenIQ 720 on the by regression calculated release profile of metronidazole/Noveon AA1 matrices. As can be seen, the release profile change in a less important manner its degree of curvature. These matrices modify in a lesser extent the release mechanism caused by the addition of different proportions of GalenIQ 720, compared to EasyTab. However, this lesser impact on the release mechanism can also be ascribed to a lesser restriction of drug dissolution. Matrices containing 40% EasyTab require 223 min to dissolve 50% of the drug while matrices containing GalenIQ 720 require 30% lesser time to dissolve the same quantity of drug, only 152 min.

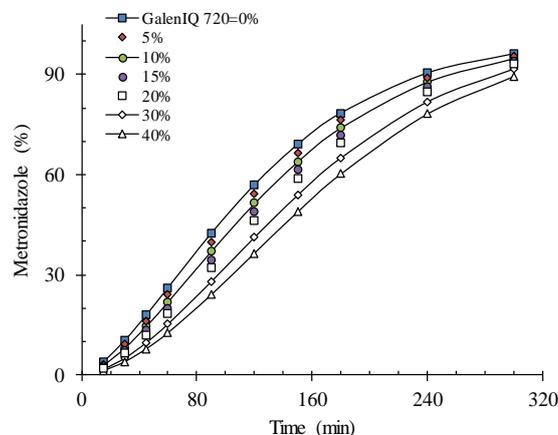


Fig. 4: Release profile of metronidazole tablets containing different proportions of GalenIQ 720 and 20% Noveon AA1, obtained from a calculated response surface

Table 3 summarizes the calculated regression parameters of release profiles of metronidazole tablets that contain different proportions of GalenIQ 721. Compared with regression parameters of tablets containing GalenIQ 720 (table 2) these results can be considered similar. The release profiles are similar, despite a lesser solubility in water of GalenIQ 720 (25 g/100 ml water), compared to GalenIQ721 (42 g/100 g water).

Table 3: Regression parameters of release profiles of metronidazole tablets containing different proportions of GalenIQ 721 and 20% Noveon AA1, calculated according to equation 1

| GalenIQ 721 (%) | Slope | Intercept | r ² | t _{50%} (min) |
|-----------------|--------|-----------|----------------|------------------------|
| 0 | 1.3447 | -6.743 | 0.9973 | 115 |
| 5 | 1.624 | -7.904 | 0.993 | 103 |
| 10 | 1.571 | -7.863 | 0.994 | 118 |
| 15 | 1.643 | -8.181 | 0.996 | 116 |
| 20 | 1.628 | -8.214 | 0.998 | 124 |
| 30 | 1.956 | -9.833 | 0.994 | 126 |
| 40 | 1.765 | -9.325 | 0.991 | 160 |

Data calculated as a whole from three dissolution curves

Fig. 5 depicts the effect of different proportions of GalenIQ 721 on the calculated release profile of metronidazole tablets containing 20% Noveon AA1. In spite of a different solubility of GalenIQ type 721 and type 720, the metronidazole release profiles cannot be considered different.

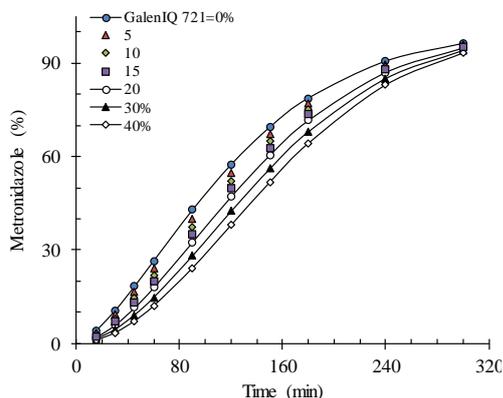


Fig. 5: Release profiles of metronidazole tablets containing different proportions of GalenIQ 721 and 20% Noveon AA1, obtained from a calculated response surface

Fig. 6 depicts the effect of different proportions of the free-flow excipients on the calculated time to attain 50% metronidazole release from tablets containing 20% Noveon AA1. This fig. shows no practical differences between the two types of GalenIQ and the greater restriction effect of EasyTab on the metronidazole release behavior.

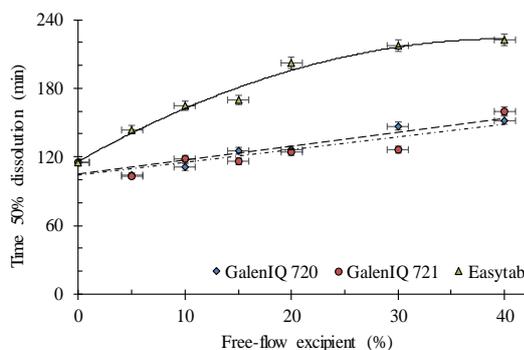


Fig. 6: Effect of different proportions of free-flow excipients on the time necessary to release 50% metronidazole from tablets containing 20% Noveon AA1, n=3

Influence of free-flow excipients on compactibility of metronidazole/Noveon AA1 tablets

A pharmaceutical tablet is a large group of particles held together by active bonds between external surfaces of particles. The compaction properties of pharmaceutical powders are characterized by their compactibility. Compactibility is defined as the ability of material to form coherent agglomerates after compression. It is quantified more frequently by a curve of tensile strength versus compression pressure (compactibility profile). Compactibility has been defined with regression parameters of equation 2 [26-27].

$$\ln\left(-\ln\left(1 - \frac{D}{D_{max}}\right)\right) = n * \ln Pc + I \quad \text{Eq. 2}$$

Where: *D* is the hardness or crushing strength of the tablets, *Dmax* is the greatest tablet hardness attained, *Pc* is the compaction pressure, *n* is the slope of the curve, and *I* is the intercept of the curve.

As can be seen in fig. 7, the use of EasyTab allows greater compactibilities of Metronidazole/Noveon mixtures, followed by GalenIQ 721 and thereafter by GalenIQ 720. In this case, using a free-flow excipient proportion of 20%. This fig. displays the experimental points and the calculated regressions with equation 2.

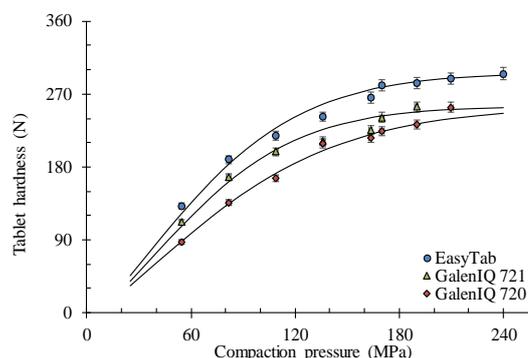


Fig. 7: Effect of 20% of different free-flow excipients on the compactibility profile of metronidazole tablets containing 20% Noveon AA1, n=3. Experimental points and calculated regressions

Table 4 summarizes the calculated regression parameters of compactibility profiles of metronidazole tablets containing different proportions of Prosolv EasyTab and a constant 20% Noveon AA1. Given the regression parameters, a response surface was constructed showing the compactibility of the mixtures with different proportions of EasyTab and compacted at different compaction pressures. Fig. 8 depicts this relationship.

Table 4: Regression parameters of compactibility profiles of metronidazole tablets containing different proportions of EasyTab and 20% Noveon AA1, calculated according to equation 2

| Easytab (%) | Slope | Intercept | r ² | TH _{136MPa} (N)* |
|-------------|-------|-----------|----------------|---------------------------|
| 0 | 0.652 | -2.993 | 0.968 | 73 |
| 5 | 1.416 | -6.398 | 0.946 | 202 |
| 10 | 1.416 | -6.209 | 0.953 | 217 |
| 15 | 1.480 | -6.617 | 0.926 | 237 |
| 20 | 1.466 | 4.490 | 0.964 | 258 |
| 30 | 1.504 | -6.771 | 0.917 | 293 |
| 40 | 1.529 | -6.680 | 0.948 | 323 |

Data calculated as a whole from three compactibility curves.* TH = tablet hardness

Fig. 8 shows an increase in tablet hardness with an increasing proportion of the free-flowing excipient EasyTab in the mixtures. The before observed properties of EasyTab as a binder [20-21] are confirmed with the current results. Furthermore, the effect of the

compaction pressure is an increasing tablet hardness as the compaction pressure increases, leveling at certain compaction pressure. The latter relationship corresponds to the second part of the sigmoid relationship described by Equation 2.

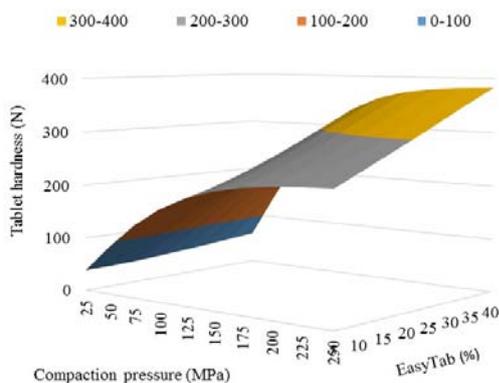


Fig. 8: Calculated response surface for compactibility of metronidazole tablets containing different proportions of EasyTab and 20% Noveon AA1

Similarly, table 5 summarizes the regression parameters of compactibility profiles of metronidazole tablets containing different proportions of GalenIQ 720 and a constant proportion of Noveon AA1 (20%). As observed by EasyTab, it can also be observed an increasing tablet hardness as the proportion of the free-flow excipient increases. However, the improvement in compactibility is clearly lesser in the case of GalenIQ 720.

Fig. 9 depicts the calculated response surface displaying the effect of compaction pressure and the proportion of GalenIQ 720 on compactibility of metronidazole/Noveon AA1 tablets. The effect of compaction pressure and GalenIQ 720 proportion is similar as

observed before by EasyTab although of a different magnitude, lesser values of tablet hardness.

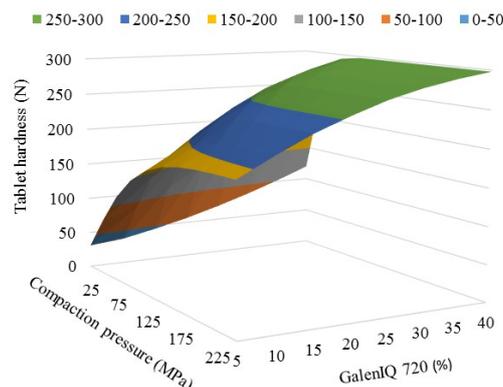


Fig. 9: Calculated response surface for compactibility of metronidazole tablets containing different proportions of GalenIQ 720 and 20% Noveon AA1

Table 6 summarizes the calculated regression parameters of compactibility curves of formulations containing different proportions of GalenIQ 721. Considering a compaction pressure of 136 MPa, tablets containing different proportions of GalenIQ 720 show an average tablet hardness of 188 N while formulations with similar proportions of GalenIQ 721 show an almost identical value, 189 N.

Table 5: Regression parameters of compactibility profiles of metronidazole tablets containing different proportions of GalenIQ 720 and 20% Noveon AA1, calculated according to equation 2

| GalenIQ 720 (%) | Slope | Intercept | r ² | TH _{136MPa} (N) |
|-----------------|-------|-----------|----------------|--------------------------|
| 0 | 0.652 | -2.993 | 0.968 | 73 |
| 5 | 1.614 | -7.196 | 0.916 | 168 |
| 10 | 1.643 | -7.497 | 0.929 | 182 |
| 15 | 1.706 | -7.844 | 0.933 | 189 |
| 20 | 1.414 | -6.511 | 0.992 | 200 |
| 30 | 1.827 | -8.330 | 0.810 | 242 |
| 40 | 2.034 | -9.183 | 0.931 | 266 |

Data calculated as a whole from three compactibility curves. * TH = tablet hardness

Table 6: Regression parameters of compactibility profiles of metronidazole tablets containing different proportions of GalenIQ 721 and 20% Noveon AA1, calculated according to equation 2

| GalenIQ 721 (%) | Slope | Intercept | r ² | *TH _{136MPa} (N) |
|-----------------|-------|-----------|----------------|---------------------------|
| 0 | 0.652 | -2.993 | 0.968 | 73 |
| 5 | 1.324 | -6.003 | 0.783 | 160 |
| 10 | 1.572 | -6.890 | 0.880 | 186 |
| 15 | 1.505 | -6.741 | 0.848 | 202 |
| 20 | 1.534 | -6.748 | 0.881 | 227 |
| 30 | 1.489 | -6.544 | 0.844 | 237 |
| 40 | 1.548 | -6.663 | 0.931 | 242 |

Data calculated as a whole from three compactibility curves.* TH = tablet hardness

Fig. 10 depicts the effect of compaction pressure and the proportion of the free-flow excipient GalenIQ 721 on the tablet hardness of metronidazole tablets containing 20% Noveon AA1. The observed relationships are similar to those observed before by GalenIQ 720.

Fig. 11 depicts the comparative compactibility displayed by formulations containing the three different free-flow excipients. Taking as a reference for compactibility the tablet hardness attained at a compaction pressure of 136 MPa, the presence of Prosolv EasyTab produces an increase in tablet hardness of about 3.5 N per unit percentage of the added excipient. On the other hand, GalenIQ produces an average increase of the tablet hardness of about 2.6 N

per unit percentage of the added excipient. In this fig., the greater compactibility of mixtures containing 20% GalenIQ 721 over those containing 20% GalenIQ 720, observed before in fig. 7, is no more perceived. The effect of both types of GalenIQ on compactibility of metronidazole/Noveon AA1 tablets is similar. These results are consistent with those published by Bolhuis [14] and differ from those published by Mužíková and Pavlasová [28], who reported a better compressible GalenIQ720 than GalenIQ721.

The greater agglutinant properties of EasyTab are mainly attributed to its high content in microcrystalline cellulose (96.5%) [20]. Compactibility of pure microcrystalline cellulose type 102 has been

observed to be 2-3 times higher than that of pure GalenIQ 720, decreasing the difference after dilution with the drug metronidazole [14]. The current results are similar showing lesser differences in compactibility, although all the time higher for tablets containing EasyTab.

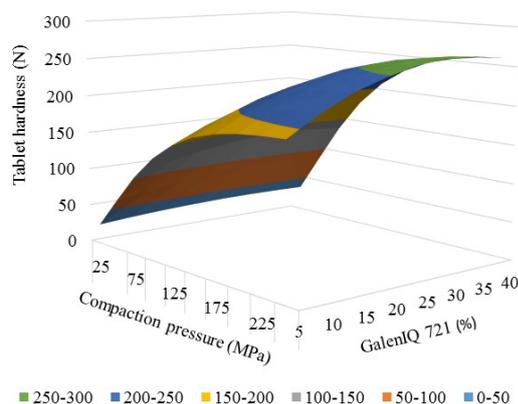


Fig. 10: Calculated response surface for compactibility of metronidazole tablets containing different proportions of GalenIQ 721 and 20% Noveon AA1

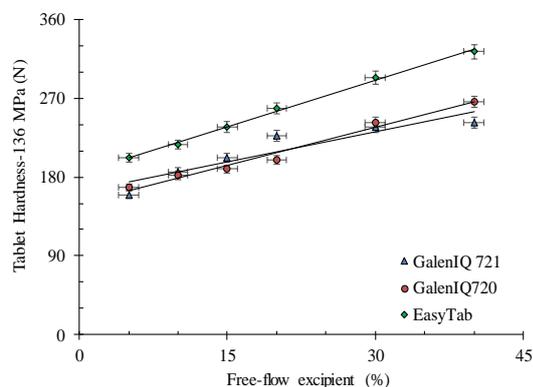


Fig. 11: Effect of different proportions of free-flow excipients on the by regression calculated tablet hardness ($P_c=136$ MPa) of metronidazole tablets containing 20% Noveon AA1, $n=3$

CONCLUSION

The aim to improve the powder flowability of mixtures of metronidazole with Noveon AA1 was not sufficiently satisfied by the addition of the free-flow excipients EasyTab and GalenIQ. The resulting powder flow rate is lesser than a half of that of microcrystalline cellulose type 102, commonly taken as reference for the minimum acceptable. Anyway, the powder flowability obtained with GalenIQ is about 20% better than that obtained with EasyTab.

The effect of the addition of the free-flow excipients on metronidazole release from tablets containing 20% Noveon AA1 is a restriction of the drug release that increases as the proportion of the free-flow excipient increases. EasyTab restricts the drug release up to a half after addition of 40% of the excipient. The EasyTab release restriction goes along with a continuing flattening of the release profile towards a zero order kinetics. This release restriction is mainly attributed to an increasing tortuosity of the drug release path as the proportion of the water-insoluble EasyTab increases. In addition, GalenIQ also produces an increasing restriction of drug release although only one third, after addition of 40% of excipient. The addition of GalenIQ does not display an important change in the release mechanism. The effect of GalenIQ on drug release restriction is attributed to competition for the available water inside the tablet. This competition occurs between the hydrating Noveon AA1 and the dissolving GalenIQ.

The compactibility of the metronidazole/Noveon AA1 mixtures increases after addition of both free-flow excipients EasyTab and GalenIQ. EasyTab increases the compactibility in about 3.5 N per unit percentage of the added excipient while GalenIQ does it in about 2.6 N.

There are no clear differences in the functioning of the powders compactibility, the rate of drug release or the powder flowability between the two types of GalenIQ.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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