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Noveon AA1 as enhancer of HPMC as a direct compression matrix for controlled release

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ABSTRACT

This work aimed the assessment of the effect of different proportions of Noveon AA1 on performance of HPMC as a controlled release agent for direct compression tablets. The functionality of polymer blends was determined using dissolution profiles, compactibility profiles and the powders compressibility index. Ten percent HPMC allows a metronidazole release after 3 h of 85%, an exponent n=0.48 and a release constant K=6.9. The increasing polymer substitution by Noveon AA1 decreases drug dissolution up to 36%, increases the exponent to 1.0 and decreases the release constant to 0.2%. The metronidazole/HPMC blend shows a slower increasing and a lower potential of tablets compactibility (20 N) while its increasing substitution by Noveon AA1 attains faster increasing and higher potential compactibilities (39 N). The metronidazole/HPMC (90:10) blend shows a low compressibility index (14%) that increases up to 33.2% with increasing Noveon AA1 proportions. Noveon AA1 proportions ≤ 5% display good/passable powder flowabilities. Noveon AA1 enhances the overall controlled release performance of HPMC, inducing zero order release patterns without lag or burst effects and reducing drug release more efficiently. Noveon AA1 also improves the compactibility of metronidazole/HPMC blends, however, decreases their flowability; flowability is acceptable only at lesser polymer proportions.

INTRODUCTION

Excipients have been classified as inert substances in a formulation, which are added with a specific purpose either to improve the conditions of production or to improve the performance of the drug. Excipients comply with various functions to optimize formulations, seeking new options to improve their effectiveness and efficiency. Excipients are useful for solving particular problems of a pharmaceutical product. To make a better selection of them, it is necessary to understand how and why they work and if they work or not in a formulation. This knowledge will allow increased probabilities to formulate in a more successful and profitable manner. Excipients are strategic tools in the evolving pharmaceutical model. However, it is necessary an appropriate selection to take full advantage of its properties and functionalities. Furthermore, its appropriate selection minimizes the risk to choose a trusted excipient with the right quality. Knowing this will help minimize operational errors and improve traceability (Monsuur *et al*., 2008). Solid dosage forms are heterogeneous systems whose performance is critical for manufacturing, transport and scaling-up of the products. Powders are difficult to be characterized, due to their own heterogeneity and tendency to segregate. This makes difficult the prediction of their functionality (Navaneethan *et al*., 2005). Functionality is the property that is desirable in an excipient to improve the conditions of manufacturing, quality or performance of a drug. Each formulation or product has its own requirements for functional excipients. However, it is also possible to determine the functionality of pure excipients to use it as a surrogate functionality. The functional performance of tablet excipients is related to their physical, chemical and technological properties. The knowledge of the surrogate functionality enables us to predict whether a particular excipient is likely to have the requisite functionality to produce a product that will meet the finished product specifications in all respects. However, only the explicit functionality of the excipients allow the development of an appropriate formulation for a specific drug and its corresponding effective manufacturing process (Díaz-Ramírez and Villafuerte-Robles, 2010).

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The application of controlled-release technologies can enhance numerous product profile attributes in a variety of ways. Controlled release applications impact on therapeutic profiles and product attributes such as efficacy, safety/tolerability, payer value, and dosage/administration and can be tailored for specific indications/populations (Solid dosage forms, 2013).

The functionality of excipients to control the release from drug delivery systems is considered relevant because it allows the knowledge of possible uses in various pharmaceutical forms, also allows understanding the mechanisms by which the carrier achieves the effect and helps to understand the possible variations that would affect the manufacture of products using this carrier (Villafuerte-Robles, 2011).

The functional tests concerning technological performance include compactibility curves, ejection pressure curves and curves displaying the disintegration properties of the individual excipients. The angle of repose, Carr's compressibility index (CI) and the Hausner ratio are further commonly used as markers of powder flowability (Nalluri and Kuentz, 2010).

The required properties that define the quality of tablets are produced through control of variables such as flowability and tabletability of the mix. This is achieved by addressing fundamental issues such as excipient choice and the concentration of each component in the final formulation (Barrios-Vázquez and Villafuerte-Robles, 2013).

Agents to control the release of drug from a tablet ideally provide not only the property to modulate the dissolution rate, but also improve the flow properties of the powders and the compactibility, avoiding a negative impact on the mechanical strength of formulations. In particular, a good compactibility and flow properties are desirable in a controlled release agent used for direct compression tablets.

Hydroxypropyl methylcellulose (HPMC) is the most widely used polymer for hydrophilic matrices. The purpose of an orally administered hydrophilic matrix is generally to prolong delivery with zero order kinetics to maintain a constant in vivo plasma drug concentration, and with this to maintain a constant pharmacological effect. HPMC possesses high sweallability, upon contact with water it diffuses into the polymeric matrix resulting in polymer chains relaxation with volume expansion. It is then that the drug diffuses out of the system. This type of systems produce mostly release profiles ranging from fickian diffusion to anomalous transport (Juárez *et al*., 2001 & Siepman and Peppas, 2012).

Methocel K4M is mentioned as a polymer that improve powder system flowability while maintaining compressibility, tablet hardness, and controlled release performance. It helps improve powder flowability to facilitate direct compression methods, taking advantage of cost savings and faster scale up when the wet granulation step can be eliminated. Methocel K4M provide greater consistency in dosage physical properties. It helps improve processing speed and predictable and consistent drug release profiles (Introducing Methocel, 2008). Noveon AA-1 is an acrylic acid polymer of high molecular weight cross-linked with divinyl glycol showing bioadhesive properties. Its application to solid dosage formulations includes its use as a controlled release polymer. It is considered that Noveon AA-1 has binding properties that provide good mechanical properties of tablet formulations, improved tablet hardness and decreased tablet friability. Noveon AA1 hygroscopicity demands processing with low relative humidity. Noveon AA1 has a very fine particle size and static loads, showing no free flowing behavior, on the other hand, segregation can occur in powder blend (Lubrizol. Guidance document, 2014).

Noveon AA1 also possess mucoadhesive properties. The concept of mucoadhesive polymers has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery systems on various membranes (Grabovac *et al*., 2005).

The aim of this work is the quantitative assessment of the effect of Noveon AA1 on HPMC performance as direct compression excipient for controlled release tablets using as a model drug metronidazole.

MATERIALS AND METHODS

The materials used in this study were Noveon AA1, obtained from Lubrizol; Hydroxypropyl methylcellulose (HPMC), Methocel K4M, obtained from Dow chemicals; metronidazole obtained from Química Alkano. The drug and the excipients were used as received

Powders to be processed

The drug and excipients were evaluated as mixtures. Corresponding amounts of the materials were weighed to obtain 30 g of mixtures of metronidazole with different proportions of Noveon-AA1: 0, 3, 5, 7, 10%, and corresponding proportions of HPMC to complete a total polymer content of 10%. The powders were transferred into a mortar and then mixed in a circular manner with pestle. The mixing method was geometrical.

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 in a Hanson Research SR6 under sink conditions, for a period of 6 hours using a paddle apparatus at 50 rpm. Each tablet was placed in a coil of stainless steel wire, to prevent sticking or floating of tablets, in 900 ml of distilled water used as the dissolution medium. For each composition, a dissolution test was performed on three individual tablets at 37 ± 0.1°C. At predetermined time intervals of 15, 30, 45, 90, 120, 180, 240, 300 and 360 minutes, samples were withdraw, filtered and evaluated with a spectrophotometer (Beckman DU 650 λ=319 nm). After each sample was withdraw, the same quantity of liquid was replaced, thus maintaining the volume in the vessel. The dissolution profile was expressed as the percentage of drug released, 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 100 MPa to 300 MPa and 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. The results were expressed as compactibility curves against the compaction pressure used to obtain the tablets.

Bulk and tapped density

The equipment used to assess the powders densities is of our own fabrication and similar to that used to determine the tap density of powders (Kibbe, 2000 & Villafuerte, 2001). The tapper was adjusted at a rate of 50 taps per minute and the graduated cylinder was elevated up to a height of 18 mm. This device uses a 100 mL graduated cylinder joined to a glass funnel with an orifice of 7 mm. The bulk (ρ_b) and tapped density (ρ_t) of powders were determined using the above-mentioned tapping machine (n=5). The 100 mL measuring cylinder was filled with 25 g of sample. The volumes were recorded at the beginning (bulk volume) and after 10 taps. The process continued until three successive volume measurements remained constant (tapped volume). The bulk density was calculated as the ratio of mass and bulk volume while the tapped density as the ratio of mass and tapped volume. The registered results are the average of five repetitions with the same sample. The powders were sieved through a number 20 mesh after each repetition. The Carr's Index or compressibility index (*CI*-%) was calculated according to the following equation (Mehta *et al*., 2012) :

$$Compressibility\ Index = \frac{\rho t - \rho b}{\rho t} * 100 \qquad \text{Eq. 1}$$

RESULTS AND DISCUSSION

Effect of Noveon AA1 on the release profile of HPMC/metronidazole tablets

The drug release from swellable matrices is mainly controlled by polymer water uptake, gel layer formation and polymeric chain relaxation. These parameters are currently regarded as primarily involved in the modulation of drug release. The use of polymers such as Noveon AA1 display 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. Drug dissolution from solid dosage forms is described with kinetic models in which the amount of drug dissolved *(Q)* is a function of test time *(t)*. In most cases, there is no theoretical concept and some empirical equations have proven to be best suited. Some analytical definitions of the function *Q (t)* include models such as zero order, first order, Hixson-Crowell, Weibull, Higuchi, Baker-Lonsdale, Korsmeyer-Peppas and Hopfenberg. These models can be used to characterize drug dissolution or the release profiles (Costa and Sousa-Lobo, 2001). In this case, the kinetics of drug release was evaluated with the aid of the exponential or Korsmayer-Peppas model (Eq. 4), which is usually used for the evaluation of drug release from matrix systems.

$$Q_t = Drug\ released = K * t^n \qquad \text{Eq. 4}$$

Where drug release is expressed as a fraction or percentage, *K* is a drug release constant incorporating structural and geometric characteristics of the dosage form and *n* an exponent indicative of the release mechanism. One major assumption of the aforementioned model is that the polymer matrix does not swell. Even if swelling does take place in many polymer carriers. However, these models are normally used to investigate a proper "fit" for the experimental measurements of drug release (Razavilar and Choi, 2013).

Figure 1 depicts the release profile of metronidazole tablets containing different proportions of Noveon AA1 and HPMC. The experimental data were treated according to the power law or exponential equation to obtain the depicted regression lines. All experimental data were used for the linear regression analysis.

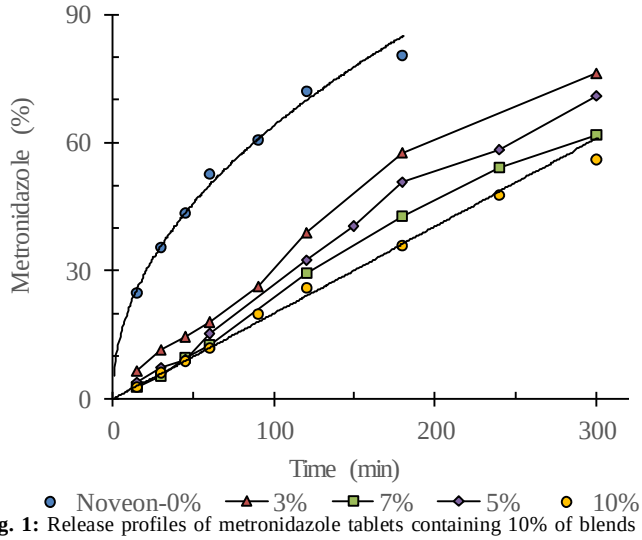

Fig. 1: Release profiles of metronidazole tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC.

Table 1: Regression parameters of release profiles of metronidazole tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC, according to the exponential model: $Q_t = K * t^n$. $ln\ Q_t = ln\ K + n * ln\ t$.

Noveon AA1 (%)	*n*	*K*	r^2	Metro 3 h (%)
0	0.4834	6.894	0.993	84.85
3	0.8618	0.5831	0.991	51.21
5	1.031	0.2166	0.993	45.80
7	1.074	0.1526	0.995	40.34
10	1.017	0.1839	0.996	36.16

Table 1 summarizes the regression parameters of release curves. An increasing proportion of Noveon AA1 produced slower release rates. Currently, the use of 10% HPMC allowed the metronidazole release after 3 h dissolution of 85%. This value decreases up to 36% after complete substitution of HPMC by

Noveon AA1. In this case, the exponent indicative of the release mechanism (*n*) corresponds with a diffusion-controlled process when the polymer is HPMC (*n*=0.48). This exponent increases gradually as the proportion of Noveon AA1 in the polymer blend increases. At Noveon AA1 proportions of 5% and higher, the exponent attains a value corresponding with a zero order release mechanism or case II-transport (average of 1.06). Noveon AA1, as a controlled release agent, is able to induce the desirable zero order release of direct compression metronidazole/HPMC tablets. The polymer blend permits HPMC proportions up to 50% of the total polymer content without losing the zero order release characteristic. This can be observed in Figure 1 comparing the degree of curvature of the release profiles. The greater degree of curvature is observed by matrices containing only HPMC while matrices containing only Noveon AA1 produce release profiles that can be perfectly described with a linear regression.

Figure 2 depicts the effect of increasing proportions of Noveon AA1 in the polymer blend, on the exponent indicative of the release mechanism (*n*). Beginning with an *n* value close to a process predominantly controlled by diffusion, it increases and stabilizes at values corresponding with a process controlled by diffusion and polymer chains relaxation.

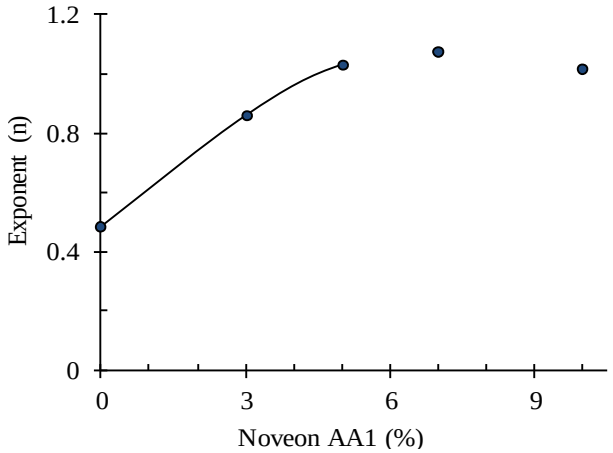

Fig. 2: Exponent (n) of release profiles of metronidazole tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC.

The dissolution burst effect, represented by the release constant (*K*) of the exponential equation, decreases gradually as the proportion of Noveon AA1 in the polymer blend increases (Figure 3). It seems that Noveon AA1 hydrates faster than HPMC, allowing a faster release control by a hydrated gel layer. HPMC needs more time to hydrate and to establish a hydrated gel layer. This allows the direct dissolution of part of the metronidazole content, without control of the polymer and its hydrated gel layer. Beginning with a metronidazole direct dissolution of approximately 7%, it almost disappear with increasing proportions of Noveon AA1 in the polymer blends, attaining values up to ≈0.2%. The consequences of the above-mentioned effects of the changing characteristics of the polymeric matrix on the drug dissolved is depicted in Figure 4.

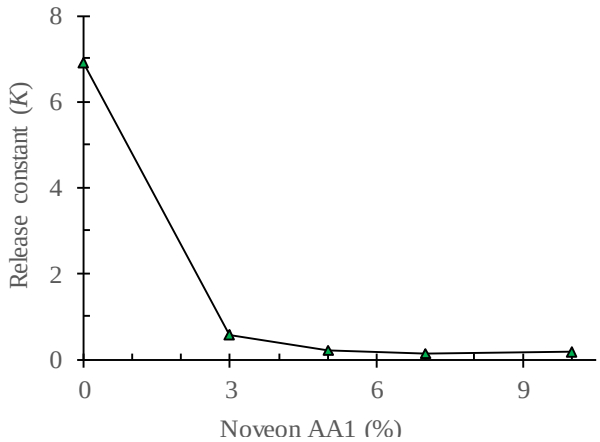

Fig. 3: Release constant (K) of release profiles of metronidazole tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC.

A direct comparison of both unmixed polymers shows that after 3 h dissolution an HPMC matrix allows 2.3 times more drug dissolution than a Noveon AA1 matrix does. Although both polymers are effective to reduce the drug dissolution, Noveon AA1 is at least two-fold more efficient to do it. The substitution of every unit of percentage of HPMC by Noveon AA1 produces an average decrease of drug dissolved after 3 h of 4.5%, in a range from 1.4% to 11.2%.

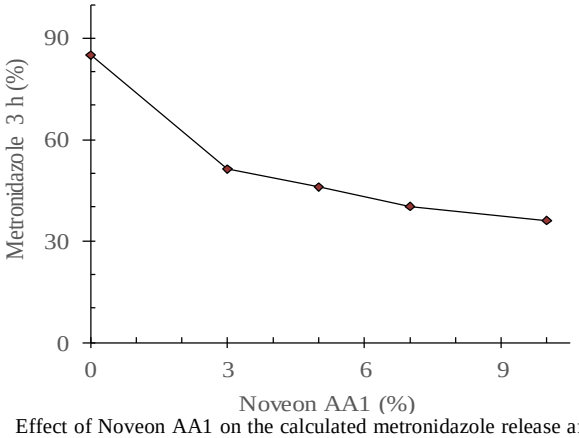

Fig. 4: Effect of Noveon AA1 on the calculated metronidazole release after 3 h from tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC.

Similar results have been observed by buccal compacts of miconazole containing Noveon AA1. The compacts displayed release profiles with a low degree of curvature and with no apparent lag or burst effects (Mohamed at al., 2011). A chitosan-Noveon AA1 complex formulated as controlled release tablets of 5-fluorouracil showed also similar release profiles, release profiles with a low degree of curvature and without burst effect (Pendekal and Tegginamat, 2012).

Effect of Noveon AA1 on compactibility of HPMC/metronidazole tablets

Selection of excipients requires a balance between efficiency in time, cost and performance expected in the product.

Excipients are included in a formulation by its properties, which together with the processes allow the production of dosage forms with the required specifications.

The tablets must have sufficient strength to resist wear or breakage during handling or processing, particularly during packing. For this reason, the hardness of the tablets is important and with practical relevance.

Figure 5 depicts the compactibility profiles of metronidazole tablets added of 10% of a polymer blend with varying proportions of HPMC and Noveon AA1. Compactability curves describe the relationship between hardness or tensile strength of the tablets and the compaction pressure used to obtain them. It is known that compactibility profiles display a sigmoid shape (Samayoa-Sandoval and Villafuerte-Robles, 2013). However, a small part of this profile can be described with a linear relationship. Figure 5 describes the experimental points and the calculated linear regressions.

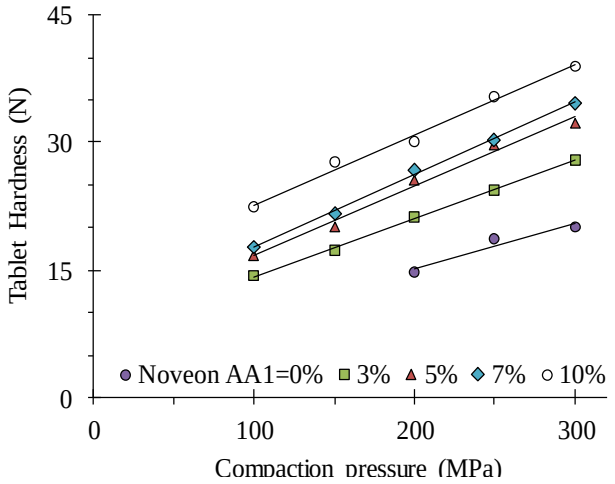

Fig. 5: Compactibility profiles of metronidazole tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC.

The slopes of compactability profiles are characteristic of the behavior of materials during compression. The slopes are related to the mechanisms that occur during the processing of the material being compacted. It is a parameter indicative of the ease or ability of a powder bed to reduce its volume and to reach a minimal porosity, when compacted. Otherwise, reflects the ease or ability of the powder bed to increase the extent or magnitude of interparticle bonds, when compacted.

In this case, the slope of compactibility profiles of metronidazole tablets containing 10% of a polymer blend with different proportions of HPMC and Noveon AA1 is described in Figure 6. The slope increases with increasing proportions of Noveon AA1 in the polymer blend up to 5%, leveling out thereafter. The ease of the powders blends to increase the interparticle bonds, responsible of the tablet hardness, increases as Noveon AA1 substitutes HPMC in the polymer blend. The rapidity to increase the interparticle bonds is about 55% faster when using Noveon AA1 than with HPMC. The slope of compactibility profiles is not related to the potential agglutinant properties of the materials but with the rapidity to form the interparticle bonds. The slope of compactibility profiles can be considered as part of the definition of the binding capacity of the materials under study.

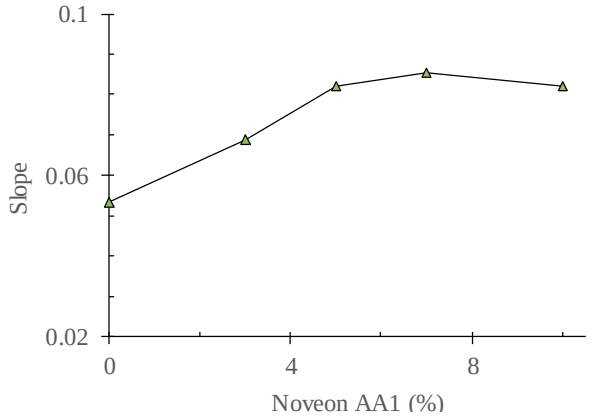

Fig. 6: After linear regression calculated slopes of compactibility profiles of metronidazole tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC.

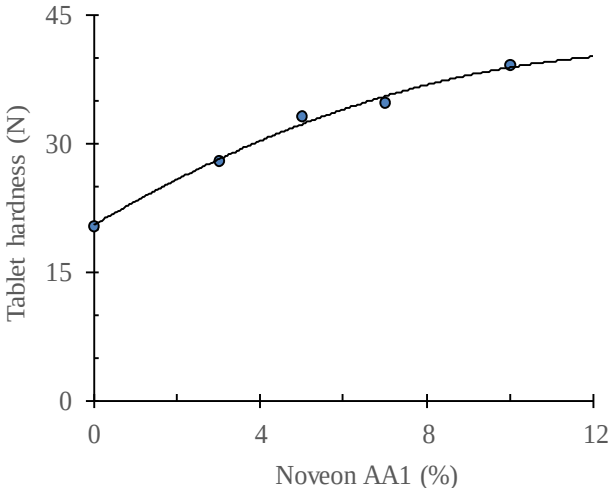

Fig. 7: Effect of Noveon AA1 on compactibility of metronidazole tablets containing 10% of blends of different proportions of Noveon AA1 and HPMC. Tablets compacted at 300 MPa.

Every value of tablet hardness or tensile strength of the Compactability profile provides a measure of the potential binding properties of that material. This information can be used as a parameter to characterize the functionality of the polymer blend to improve the poor compactibility of metronidazole. Tablet hardness can be obtained as the average of the three determinations made at every investigated compaction pressure. However, in a more reliable way it can be calculated by regression. This value is supported by the full Compactability profile. Considering a compaction pressure of 300 MPa, the calculated compactibility of metronidazole tablets containing 10% polymer blend increases continuously as the proportion of Noveon AA1 in the polymer blend increases (Figure 7). The compactibility of metronidazole tablets containing 10% HPMC shows a tablet hardness of 20.4 N

and increases to 39.1 N when HPMC is fully substituted by Noveon AA1. The compactibility of metronidazole/HPMC matrix tablets increases in an average of 1.8 N per percentage point of HPMC substituted by Noveon AA1. The functionality of Noveon AA1 is almost the double than that of HPMC as a direct compression agglutinant.

Effect of Noveon AA1 on flowability of HPMC/metronidazole powder blends

Powder flow is critical during tableting, as powders must flow easily and uniformly into the tablet dies to ensure tablet weight uniformity and tablets with consistent and reproducible properties. Interparticle forces and the packing structure mainly determine the behavior of powders. Higher compressibility index values corresponding with higher interparticle forces and/or denser packing. The compressibility index is inversely proportional to flowability of powders.

Noveon AA1 exhibits a high compressibility index (39%) and a quite slow powder flow 0.0372 g/s. It indicates an exceedingly poor powder flowability. Compared to some other excipients Noveon AA1 can be considered dysfunctional in this respect. Compressibility index of microcrystalline cellulose type 102 (Helmcel 200 is 21.7%, indicating a passable powder flowability while the compressibility index of agglomerated isomaltose (GalenIQ 720) was determined to be 13.8%, indicating a good powder flowability (Fuentes-Gonzales and Villafuerte-Robles, 2014).

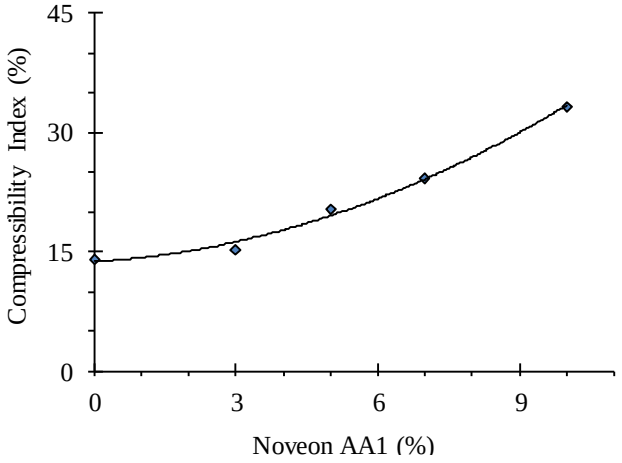

Fig. 8: Compressibility index of metronidazole blends with 10% of a polymer blend containing different proportions of Noveon AA1 and HPMC.

Figure 8 depicts the change in the compressibility index of metronidazole/HPMC powder blends after addition of different proportions of Noveon AA1. It is observed a progressive increase in compressibility index as the proportion of Noveon AA1 increases, which stands for a decrease in flowability. The material with the higher compressibility index and the lower flowability, Noveon AA1, decreases progressively the flowability of metronidazole/HPMC powder blends. The addition of 10% Noveon AA1 to metronidazole produce powder blends with a compressibility index of 33.2%. Considering that microcrystalline cellulose type 102 is at the limit of processability of powders in a high-speed tableting machine. The compressibility index suggests that the blend of metronidazole/Noveon AA1 is not processable as itself in such type of tableting machines. On the other hand, the blend of metronidazole/HPMC shows a compressibility index of 14.1%, suggesting a good powder flowability.

Figure 8 shows that additions of Noveon AA1 ≤ 5% to blends of metronidazole/HPMC could be processable, considering a compressibility index ≤ 20.2%. Higher proportions of Noveon AA1 would be dysfunctional with respect to powder flowability.

CONCLUSION

Noveon AA1 enhances the functionality of HPMC as a controlled release agent used for direct compression. Noveon AA1 displays very good controlled release properties, it induces zero order release patterns without lag or burst effects. It enhances the well-known release behavior produced by HPMC, predominantly controlled by a diffusion process, with a burst effect due to its slow hydration. The HPMC efficiency to reduce the drug release rate is also enhanced with Noveon AA1, it reduces the release rate more than the double that HPMC does. The admixture of Noveon AA1 improves the overall efficiency of the HPMC controlled release performance.

As a direct compression agglutinant, Noveon AA1 also improves the functionality of HPMC, Metronidazole/HPMC tablets display compactibilities about a half of those tablets containing Noveon AA1.

The admixture of Noveon AA1 increases progressively the compactibility of metronidazole/HPMC tablets.

Noveon AA1 exhibits a so high compressibility index that suggests an exceedingly poor powder flowability. Noveon AA1 affects negatively the rheological properties of metronidazole. The use of increasing proportions of Noveon AA1 deteriorates the flowability of metronidazole/HPMC powder blends. The use of Noveon AA1 proportions ≤5% seems to be at the limit to process metronidazole/HPMC powder blends in high speed tableting machines. The use of Noveon AA1 in proportions >5% could be considered dysfunctional. In this case, powder flowability has to be corrected with other excipients to make processable metronidazole/HPMC powder blends.

Declaration of interest

The authors declare no conflict of interest.

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