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Abstract

Methyl ester derivatives of alginic acid have been evaluated as potential multifunctional excipients for pharmaceutical direct compression. The use of alginic acid as an excipient in tablet formulation is limited because of certain drawbacks such as low tablet hardness and poor compressibility. The objective of this work is to improve these properties through esterification of alginic acid, chemical modification commonly used for enhancing the functionality of tableting excipients. It has been observed that the degree of methylation (DM) has a profitable impact in the physico-chemical and mechanical properties of the obtained materials. In general, an increase in the degree of methylation yielded tablets with higher tensile strength and better compressibility. Furthermore, modified alginates exhibited extended disintegration times compared to native alginic acid due to the introduced hydrophobicity. Finally, the functional versatility of the modified alginates as disintegrating and filling/binding agents was tested by formulating them with microcrystalline cellulose and lactose.

Key Words: alginic acid, polysaccharide, degree of methylation, direct compression, multifunctional excipient.

1. Introduction

The oral route of drug administration is the most convenient for patients, with tablets being the popular solid oral dosage form. Tablets have numerous advantages over other dosage forms such as, ease of administration, high level of patient compliance and possibility of modifying the release of the active pharmaceutical ingredient (Augsburger et al. 2008). A topic presenting increase interest in pharmaceutical research is the development of materials displaying multifunctional properties for the conception of directly compressible excipients for tablet's production (Saha et al. 2009). Polymers based on natural resources are one of the platform materials with highest potential to develop novel excipients designed to perform specific functions, thanks to their abundance, biodegradability and nontoxicity (Hamman 2010; Li et al. 2014).

In this framework, alginic acid and its salts, emerge as an excellent choice to develop added-value materials for tableting and drug delivery applications. These materials are versatile in their applications;

Abbreviations: AA – Alginic acid; MeA – Methyl alginate; DM – Degree of methylation; DT – Disintegration time; TS – Tensile strength.

while alginate hydrogels have been particularly attractive in wound healing, drug delivery and tissue engineering (Sanchez-Ballester et al. 2019; Schmid et al. 2009). Alginic acid shows interesting properties as excipient promoting disintegration in tablets designed for immediate drug release (Tonnesen et al. 2002; Soulairol et al. 2018). Despite the proven interest, the use of these materials remains limited due to certain fall-backs such as non-controlled swelling properties, low tablet hardness and poor powder flowability.

The preparation of polysaccharide derivatives is a good way to alter the properties of the initial polysaccharide to develop materials with desired properties (Xie et al. 2020). For example, the introduction of different length fatty acids to chitosan by *N*-acylation successfully modified tablet strength and swelling behaviour due to an enhance of stability of the substituted chitosan *via* hydrophobic self-assembly (Le Tien et al. 2003). Another well-known method to change the properties of pharmaceutical excipients is by esterification. For instance, cellulose esters are widely used in pharmaceutical controlled release preparations and for the development of micro-porous delivery membranes and bioadhesives (Edgar 2007; Hiorth et al. 2014). Esterification of starches has also been used to improve their functional limitations as pharmaceutical excipients (Ačkar et al. 2015). Modified starches presented better rheological and mechanical properties, as well as sustained-release delivery due to the introduced steric bulkiness and hydrophobicity which extends the drug release in dissolution media (Lawal 2019). Likewise, low- and high-methylated pectins have shown extended interest as tableting excipients and drug carriers (Salbu et al. 2010). This interest comes from the attractive physico-chemical properties' pectins possess such as, muco-adhesiveness, degradation stability against proteases and amylases of the upper gastrointestinal tract and ease of forming gels in acid environments (Minzanova et al. 2018).

Alginate-ester derivatives in which methyl, ethyl and isopropyl residues were grafted onto the polysaccharide backbone *via* ester groups have been previously described in the literature (Taubner et al. 2017; Murdzheva et al. 2016; Broderick et al. 2006). These studies highlighted the potential significance of these materials for the encapsulation of both hydrophilic and hydrophobic molecules, while retaining the gelling and non-toxic properties of native alginates. Alginate derivatives have been also considered for the controlled release of encapsulated proteins such as, *H. pylori urease* achieved by addition of esterases which hydrolyze the ester bond or by addition of surfactants which induce the dissociation of the intermolecular hydrophobic network (Leonard et al. 2004). However, although its sufficiently demonstrated broad interest in medical and pharmaceutical research, none attention has been addressed to the potential use of alginate-esters as excipients for direct compression.

Therefore, the present work is aimed to evaluate the aptitude of methyl esters derivatives, obtained from chemical modification of alginic acid, as excipients for pharmaceutical direct compression. The impact of the degree of methylation on the physico-chemical and mechanical properties was assessed in order to obtain a better understanding of the structure-properties relationship. The presence of the methylated group is expected to induce modular hydrophobic character and to improve some of the drawbacks shown by the alginic acid as tableting excipient such as, low tablet hardness.

2. Materials and Methods

2.1 Materials

Methylated alginates were prepared from alginic acid (AA; CAS 9005-32-7; Lot SLBT2973) (Sigma-Aldrich, Germany) with 43% in guluronic acid and presenting an organization in block of their polysaccharides chains. The main characteristics of the alginic acid used in this study were determined by routine ^{1}H liquid-state NMR analysis and are the following: the respective fraction of mannuronate (F_M) and guluronate (F_G) in the alginate backbone (F_M: 0.57; F_G: 0.43; F_{MM}: 0.45; F_{MG}-F_{GM}: 0.12; F_{GG}: 0.31); the η parameter, which describes the alternation of M and G groups, is equal to 0.49 which corresponds to a sequenced block-copolymer; the N_G, that represent the average number G units in G-blocks equal to 4. The samples were prepared as described previously by Grasdalen (Grasdalen et al. 1979). Sulfuric acid 96% was purchased from Sigma-Aldrich. Distilled water was used for the preparation of all solutions.

Lactose (Excipress™ 2SD, Lot X19176003 Armor Pharma, France) and microcrystalline cellulose (MCC) (Vivapur® 200, Lot 56200190504 JRS Pharma, USA) were used as directly compressible filler binder excipients. Magnesium stearate (MgSt) (Barlocher-Wiga Pharma GmbH, Lot 600017 Germany) was used as lubricant.

2.2 Preparation of methyl ester alginic acid

Alginic acid was esterified following a method previously reported with methanol in the presence of sulfuric acid (Taubner et al. 2017). Alginic acid (1 g) was suspended in 200 ml of methanol containing 1 mL of concentrated 96% sulfuric acid. The reaction was carried out under heterogeneous conditions with magnetic stirring at 60 °C at different intervals of time: 1, 2, 4, 8, and 24 h. The solid reaction product was filtered, washed with 25 ml of ethanol and 25 ml of acetone and dried in the oven at 40 °C. The reaction yield of the methyl esterification was 62-76%. Products were stored at 25°C and 50% relative humidity.

2.3 Physicochemical characterization

2.3.1 FTIR

All spectra were recorded from 4000–600 cm^{-1} using a FT-IR Nexus spectrometer DuraSamplIR II equipped with an in-compartment diamond ATR accessory. The IR data were treated and stored using Spectrum software OMNIC (5.0) (Thermo-fisher Scientific, USA). All spectra were scanned at room temperature in transmission mode with a scan speed of 0.20 cm/s, and 4 accumulations at a resolution of 4 cm^{-1}.

2.3.2 X-ray Diffraction

Powder X-ray diffraction (XRD) patterns were recorded using a Bruker D8 Advance diffractometer and the monochromatic Cu Kα1 radiation (λα = 1.5406 Å, 40 kV and 40 mA). They were recorded with 0.02° (2Θ) steps over the 10-80° 2Θ angular range with 0.1s counting time per step using LINXEYE detector 1D.

2.3.3 Scanning Electron Microscopy

Particles morphology was investigated by Scanning Electron Microscopy (Hitachi 4800 S, Japan) after platinum sputtering under vacuum before observation.

2.3.4 Thermal gravimetric analysis

Composition and thermal behavior were evaluated on 10 to 20 mg samples weighed in a ceramic pan, by Thermal Gravimetric Analysis (TGA, STA 6000, Perkin Elmer) from 30 to 600 °C at a heating rate of 15 °C/min under airflow.

2.3.5 ^{13}C solid-state NMR

$^{13}C\{^{1}H\}$ NMR spectra of powdered solids were recorded on a Agilent-Varian VNMRS 300 spectrometer fitted with a HX 7.5 mm MAS probe. Further experimental details are detailed in Supplementary Information section.

2.3.6 True density

True density of the dried powders was measured using a helium pycnometer 1305 (Micromeritics, USA) and the required mass of powder for each measurement was about 3 g. Measurements were done in triplicate for each sample.

2.4 Compaction study

2.4.1 Tabletability

Pharmaceutical tablets of 25 mg of each material were compressed using a rotary tablet press simulator Styl'One Evolution (using Analis software, Medelpharm, France) at different compaction pressures (100, 200, 300 and 400 MPa). Flat punches of 3 mm diameter were used for the compaction study and the speed rate was of 10 tablets/min. Styl'One comprises one compaction station with a system of punch displacement control. The tare of the force sensors was done automatically and the tare of the displacement transducers was performed using the "standard" mode using a gage block of 1 mm, before starting each acquisition.

Tablets of 400 mg were compacted at 100, 200 and 300 MPa compaction pressures. Flat punches of 11.28 mm diameter were used for the compaction study and the speed rate was of 10 tablets /min. Tablets tensile strength was calculated using hardness, thickness and diameter data measured using a Sotax Multitest 50FT (Sotax AG, Switzerland).

The diametric tensile strength (TS) was calculated from the crushing force using the following equation (1):

$$TS=2F/\pi Dh \qquad (1)$$

Where F is the diametric force necessary to break the cylindrical compact, D the diameter of the compact and h its thickness, its value accurately expresses the powder tabletability.

2.4.2 Compressibility

Compressibility of alginates was evaluated by the measurement of tablet porosity according to equation (2)

$$\varepsilon = 1 - \rho r \qquad (2)$$

In which the relative porosity (ρr) is calculated according to equations (3) and (4):

$$\rho r = \rho Ta / \rho Tr \qquad (3)$$

$$\rho r = mT / \pi R^2 hT \rho Tr \qquad (4)$$

Where ρTa is the density of tablet, ρTr true density, R the radius of tablet, hT its height and mT its mass.

2.4.3 Heckel and Walker modeling

For Heckel modeling, three tablets compacted of the studied materials, at 200 MPa, were used. They presented a constant mass of 400 mg. True densities (ρ) measured previously with the helium pycnometer (Table S1 Supplementary Information) were used to calculate Heckel mean yield pressures (Py) which are given by the inverse values of the slope of the following equation 5:

$$Ln\left(\frac{1}{1-D}\right) = \mathrm{K}P + \mathrm{A} \qquad (5)$$

K is the slope of the linear part of the plot (with the best R^2 fit). A is the Y axis intercept with the linear part of the Heckel plot. Hersey and Rees defined that Py values can be used to characterize the deformation mechanism of materials (Hersay et al. 1971). For them, the low value of Py reflects the plastic deformation of a hard ductile powder while Py high value reflects a fragmentary deformation of a brittle material under compaction force. Heckel equation was fitted for all the materials using data collected from in-die compaction experiments. The fitting of the models was performed using regression by minimization of the sum of squared errors. The software Analis (Medelpharm, France) was used for the fitting of the model. Qualitative assessment was made to select the most central part of the linear region. The regression coefficient was then calculated for this selected region.

For Walker modeling, true density is also used to determine the evolution of the powder relative volume with the increase of the compaction pressure, Walker defines « W » as the compressibility coefficient which represents the slope of the following equation 6:

$$100V = -W * log(p) + \mathrm{C} \qquad (6)$$

Where, V is the relative volume, P is the compaction pressure and the constant C. The compressibility coefficient « *W* » indicates a measure of the irreversible compressibility of the compact, higher is the W value, better is the compressibility of the powder. This model is more robust and more repeatable than

Heckel but less accurate. For this study, lactose and microcrystalline cellulose were also used as reference materials to interpret the deformation mechanism of alginic acid and methylated derivatives.

2.5 Disintegration time *in vitro*

A modified disintegration prototype apparatus was developed in house to evaluate the disintegration time (DT) of the mini-tablets produced. The tested tablets were manufactured at similar tensile strength. The design of this device is inspired by the experimental setup previously described which applies a constant force on the tablet during the disintegration (Abdelbary et al. 2005). The tablet is placed on a filter paper and a force of 0.5 N is applied by a cantilever to the top surface of the tablet. Then, 1 mL of distilled water is added onto the filter paper and a stopwatch is started. When the cantilever stops displacement, the disintegration is considered completed and the stopwatch is stopped to record the time. Each test was repeated 5 times and results are expressed as the mean value ± standard deviation.

The disintegration tests for 400 mg tablets were performed according to the European Pharmacopeia guidelines using a disintegration apparatus (Sotax, DissiTest50, Switzerland). Six tablets of each formulation were tested simultaneously and the results expressed as the mean value ± standard deviation. The end point was achieved when no residues were present on the bottom of the test basket as described in the European Pharmacopeia.

3. Results and discussion

In this work commercial alginic acid was chosen as starting material for the targeted modification as it has been described more suitable than sodium alginate for a direct esterification (Taubner et al. 2017). Alginate backbone possess two available functional group types that can be used for derivatization, –COOH and –OH groups. Selective reaction of charged carboxylate (COO^-) over neutral hydroxyl groups is advantaged, since the former is a stronger nucleophile. The difference in nucleophilicity can be used to selectively react the carboxylate groups with substrates that can undergo S_N2 substitution (Pawar et al. 2013).

The esterification of alginic acid with methanol was performed under heterogeneous conditions using acid catalysis, so this process depended on the surface interaction between the solid phase (polysaccharide suspension) and the liquid medium (methanol/H^+). As native AA, all methylated derivatives obtained are insoluble in water.

3.1 Physico-chemical characterization

The degree of methylation (DM) of alginic acid was determined by solid-state ^{13}C NMR (Figure 1). Essentially, a gradual increase in DM as a function of time is observed.

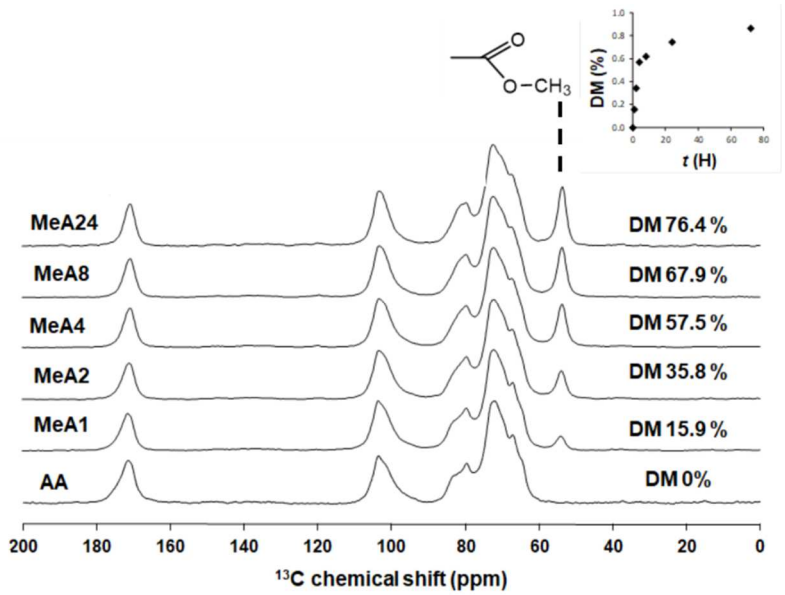

Figure 1. Solid-state $^{13}C\{^{1}H\}$ CP-MAS NMR spectra of alginic acid (t_c = 1.5 ms) and methyl alginate materials (t_c = 1.0 ms) obtained at different esterification times., respectively. DM – Degree of methylation; AA – Alginic acid; MeA – methyl alginate.

The degree of esterification/reaction time relationship was also corroborated by FTIR as shown in Figure S1 (Supplementary Information).

Figure S2 (Supplementary Information) shows the SEM images of the methylated materials obtained at different reaction times compared with alginic acid starting material. All materials are composed of particles presenting heterogeneous morphologies, where elongated and more rounded particles co-occur. No evident differences in the morphology and the size of the particles were observed after methylation. These observations can be explained by the heterogeneous reaction conditions used to obtain the methylated derivatives.

In general, *p*XRD patterns exhibit broad diffraction peaks, consistent with alginate amorphous structure presenting some extends of higher structural order (Figure 2). Closer examination of the XRD patterns showed the characteristic three diffraction peaks at 14.3, 15.2 and 20.9° for alginic acid followed by a broad peak. These results are in agreement with several studies reported on the atomic structure of alginic acid (Cheong et al. 2008). Higher DM increased the intensity of the peak at 20.9° which also became slightly sharper. Moreover, while peak at 14.3° disappeared for highly methylated materials, a new peak at 8.9° occurred. Thus, the DM seems to have an effect in the organization of the alginate chains. It is worth noting that the structural organization of polysaccharides can play a key role in their mechanical properties (Le Tien et al. 2003).

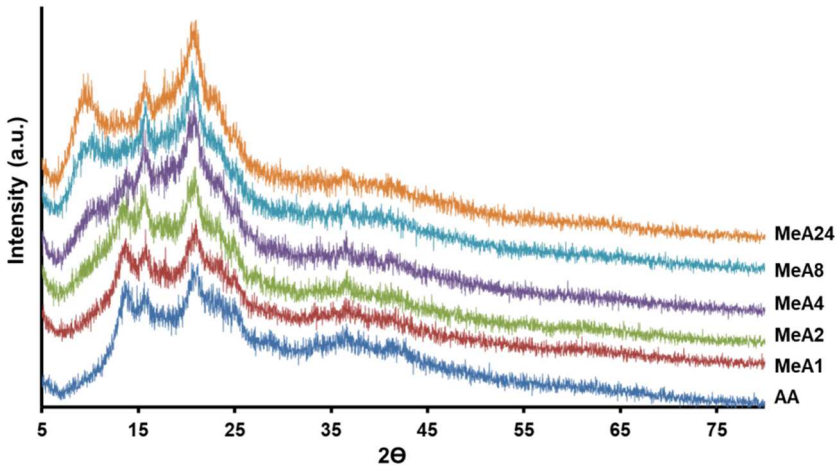

Figure 2. XRD patterns of alginic acid and modified alginates presented in this study.

The obtained MeA powders were thermally characterized and compared to native alginic acid using TGA analysis. In general, thermal stability of the methylated compounds increases with the degree of methylation (Figure S3 S.I.).

Distinctly, esterification can be described as a simple and effective method for introducing new functional groups that change the physico-chemical properties of alginic acid. Now it is essential that these modifications also have an influence in the tableting properties. Specially enhancing tablet properties such as, tablet hardness and compressibility, functional characters not inherently present in native alginic acid.

3.2 Functionality Study

3.2.1 Pure powders

Heckel and Walker equations were used to analyze the compressional properties of the modified products. Table 1 shows the variation of the mean yield pressure Py obtained from Heckel model as a function of compaction pressure for alginic acid and the methylated materials. The deformation mechanism of each material was compared to two references, lactose and MCC that are known as brittle and plastic materials, respectively. Py is inversely proportional to the ability of powder to deform plastically.

Table 1. Parameters derived from Heckel and Walker models.

Material	Py (MPa)	W
Lactose	127.5 ± 0.7	40.1 ± 0.3
MCC	47.5 ± 0.2	83.1 ± 0.1
Alginic acid	115.1 ± 0.4	53.8 ± 0.2
MeA2	72.2 ± 0.5	62.4 ± 0.1
MeA4	68.1 ± 0.1	68.8 ± 0.2
MeA8	63.5 ± 0.4	67.9 ± 0.2

MeA24	64.7 ± 0.2	67.5 ± 0.2

Alginic acid presents a Py value lower than that of lactose but higher than MCC meaning that it can be consider more a brittle than a ductile material. Py values for alginic acid derivatives decreased with the degree of methylation. Thus, the lowest Py values were observed for MeA8 and MeA24, materials presenting the higher degrees of methylation. This suggests that esterification induced greater plastic deformation mechanism than that observed for native alginic acid.

For Walker modeling, MCC presented the higher W values and lactose exhibited the lower W values. While alginic acid showed intermediate results with W values closer to lactose, the W values for methylated materials were closer to those of cellulose.

As previously mentioned, alginic acid shows interesting properties as disintegrating excipient but its limited employment is associated to its low tabletability. It must be pointed out that this change in the deformation behavior of the modified materials can be important for enhancing tabletability. Pertinent correlations between improvement of the compact mechanical properties with the type of excipient's deformation mechanism (brittle or ductile) have been already described by other authors (Narayan et al. 2003; Lawal et al. 2015).

Tabletability is the capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure (Sun et al. 2001). It is represented by a plot of the tensile strength (TS) versus compaction pressure. The TS is influenced on the one hand by the compression pressure and on the other hand by the material properties of the material or formulation used. Figure 3 (A) shows the tensile strength of alginic acid and methylated materials mini-tablets compressed at different compaction pressures. Mini-tablets were chosen for the compaction study due to the small quantities of powder obtained by the published synthetic protocol. Currently an optimized scale-up synthetic path is being developed. To eliminate the influence of the particle size, the different materials were fractionated and the same fraction of each type (< 250 µm) was compressed. Furthermore, the experimental conditions such as, compaction rates were identical during this study.

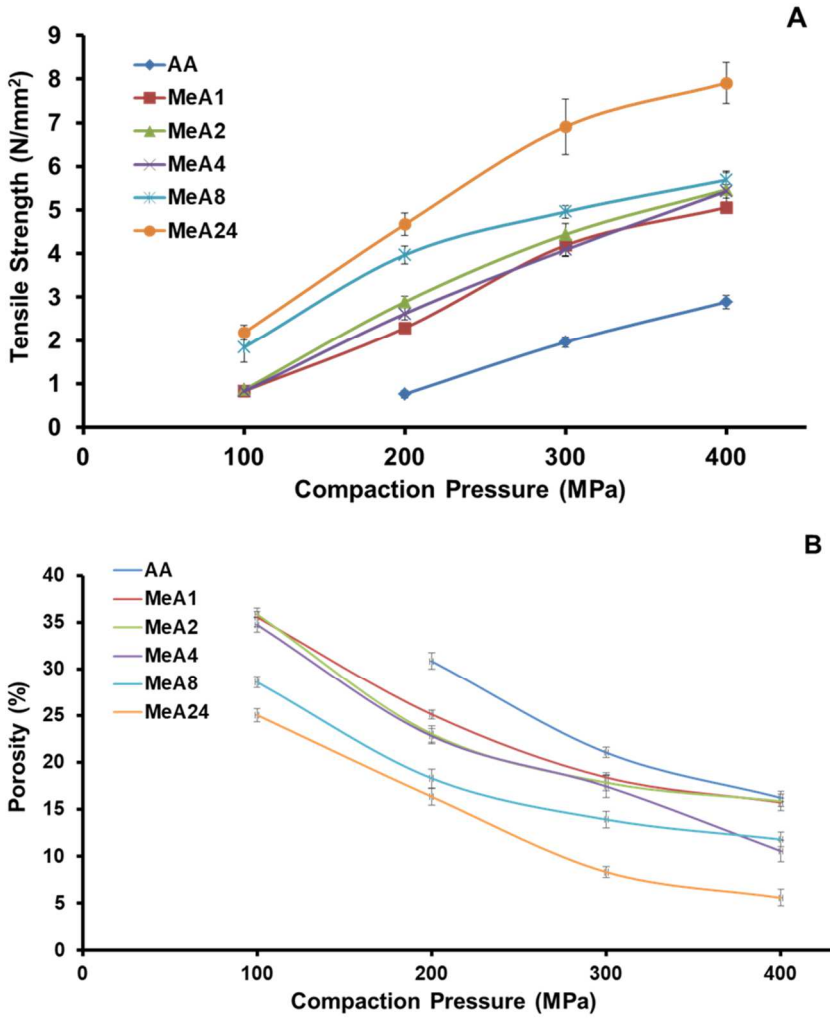

Figure 3. Curves of tensile strength (A) and porosity (B) as function of compaction pressure for pure AA and methylated powders.

In general, TS increases with the degree of methylation. Mini-tablets obtained with alginic acid possess the lower tensile strength at all compression pressures. It is important to highlight that tablets of AA could not be obtained at 100 MPa. Although no significant difference in tensile strength was observed between MeA obtained at 1, 2 and 4 hours, the DM clearly seems to play an important role in the mechanical properties of the methylated systems. Thus, tablets presenting the highest values for TS were obtained for MeA24.

This trend was also corroborated by the profiles of compressibility represented by a plot showing the reduction of tablet porosity with increasing compaction pressure (Figure 3 B). Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure. Thus, it was observed that while alginic acid mini-tablets presented the highest porosity at all compaction pressures which leads to a decrease in hardness. MeA24 presented the lowest values of porosity and therefore the ability to form hard cohesive tablets. This higher tendency of MeA24 to change porosity with pressure is a typical behavior observed in ductile materials (Zhao et al. 2006).

Different and potentially cooperative factors can explain the higher tensile strength observed in mini-tablets obtained with pure methylated materials. First of all, this enhancement in TS can be due to the increased plastic deformation observed in the esterified powders. A similar trend to our findings was observed in the plastic deformation-compactability relationship of methoxylated pectins. Higher degree of methoxylation also resulted in stronger pectin's compacts (Kim et al. 1998).

Furthermore, it can be postulated that the changes observed in the structural organisation of AA and methylated derivatives may also contribute to the differences observed in tensile strength. A similar increase in the crushing strength of tablets has been described in acyl-chitosan derivatives with fatty acids of different chain length. The better mechanical properties observed were interpreted by an enhancement of the stability due to hydrophobic interactions which seem to participate in the self-assembled network organisation (Le Tien et al. 2003).

It should be also pointed out that the fact of producing tablets with high hardness levels, comparable to pure MCC (8.7 N/mm^2 at 400 MPa) (Formulation Part), especially for MeA24 (7.9 N/mm^2 at 400 MPa), make these materials interesting candidates for being used as direct compression fillers/binders.

Also noteworthy is the difference observed in the values of minimum distance between the punches measured for the different powders at comparable compression force (Figure 4).

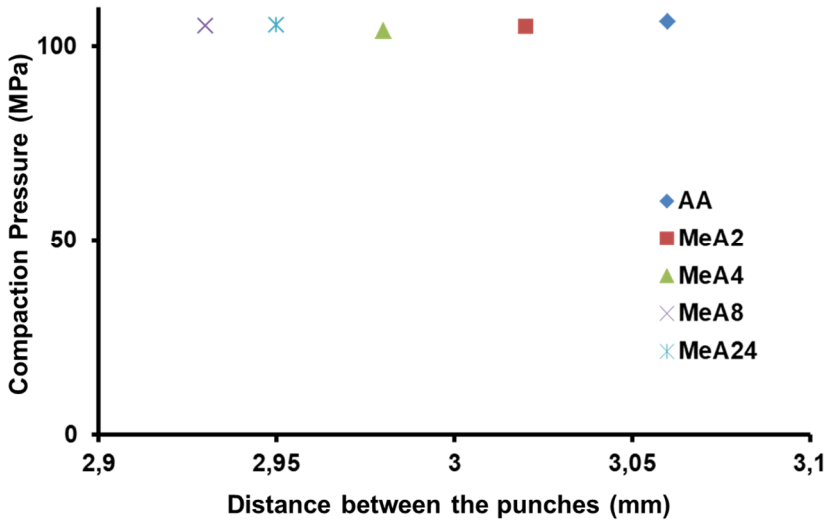

Figure 4. Minimum distance between the punches measured for the different powders at comparable compression force.

While the alginic acid exhibited the highest distance value, these values decreased as one moves towards higher degrees of methylation. This decrease in distance implies that rearrangement ability of the particles in the peak of compression increases with the degree of methylation. These results corroborate an interesting experimental observation regarding the easier filling of the die with the modified alginates compared to AA, indicating that the methylated powders seem to exhibit more free-flowing properties than native alginic acid. The apparent increase in flowability cannot be explained by

a physical factor such as, particle size and morphology, as they are not being altered after esterification (Figure 2S SEM) but rather due to interparticular interactions, such as hydrogen bonding which can induce agglomeration. Mention that an agglomerated powder can form cohesive clusters which may not pack especially well (Spierings et al. 2016). Further scale-up will allow demonstrating the ameliorated observed flowability by performing bulk and tapped density measurements.

3.2.2 Disintegration times

The values of disintegration time for alginic acid and methylated derivatives mini-tablets are shown in Figure 5A. In order to examine the effect of the methylation in the disintegration time, tablets possessing similar tensile strength were produced for all the materials under study. As the tensile strength was kept constant the resulting differences in DT are mainly driven by the excipients.

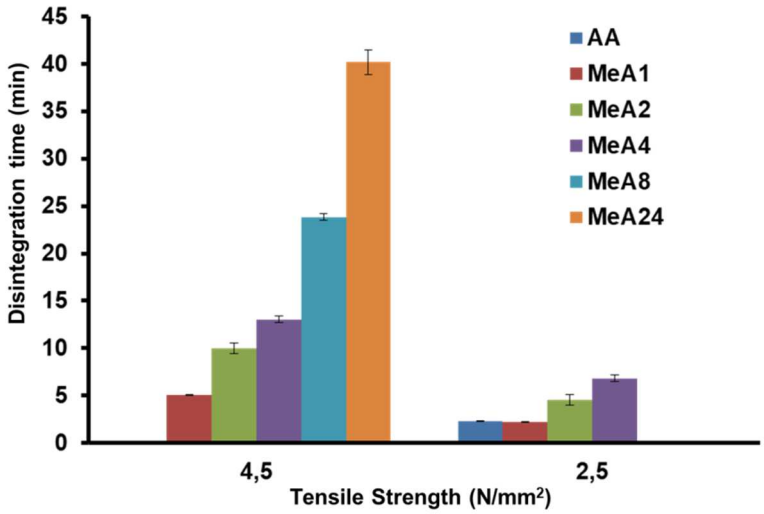

Figure 5. Disintegration times for mini-tablets at 2.5 and 4.5 N/mm^2 for AA and methylated derivatives.

It was found that disintegration time increases with the degree of esterification. As the disintegration time of AA has been found not to be correlated to the swelling force but mainly related to the water uptake kinetics (Soulairol et al. 2018), the higher DT values observed on the modified alginates may be attributed to an enhancement in hydrophobicity with increased methylation. While AA, MeA1, MeA2 and MeA4 presented DT in accordance with disintegrate excipients (< 15 minutes), MeA8 and MeA24 presented longer disintegration times (24 and 42 minutes, respectively). It is interesting to remark that a similar trend was obtained for the disintegration times of 11.28 mm tablets (Figure S4 Supplementary Information). These results suggest that these materials could be consider as potential candidates for designing *on demand* release dosage forms for moisture sensitive drugs; immediate release for MeA1, MeA2 and MeA4 and (less than 15 min) and sustained release for MeA8 and MeA24 (European Pharmacopoeia. 9th Ed.). Excipient's hydrophobicity has been already shown to have an impact on the inhibition ability of drug hydration (Paisana et al. 2015).

3.3 Formulation

Each material was formulated at different contents (5, 10 and 20%) with MCC and lactose in order to evaluate the effect of the addition of these excipients on mini-tablet's hardness and disintegration time. This permitted also to evaluate the potential of these materials to perform multiple functions as tablet formulation excipients.

Figure 6 shows that while the addition of AA and methylated compounds at low content (5 %) to the targeted diluents/binders has little influence in the hardness of the mini-tablets (A and B); as expected, an increase of these materials in the content formulation has a more marking effect in the tensile strength of the tablets (Figure 6 C and D). The increase in tablet's hardness observed in the formulations with lactose can be explained by the greater plastic deformation under compaction shown by alginic acid and methylated derivatives compared to lactose (Nachaegari et al. 2004).

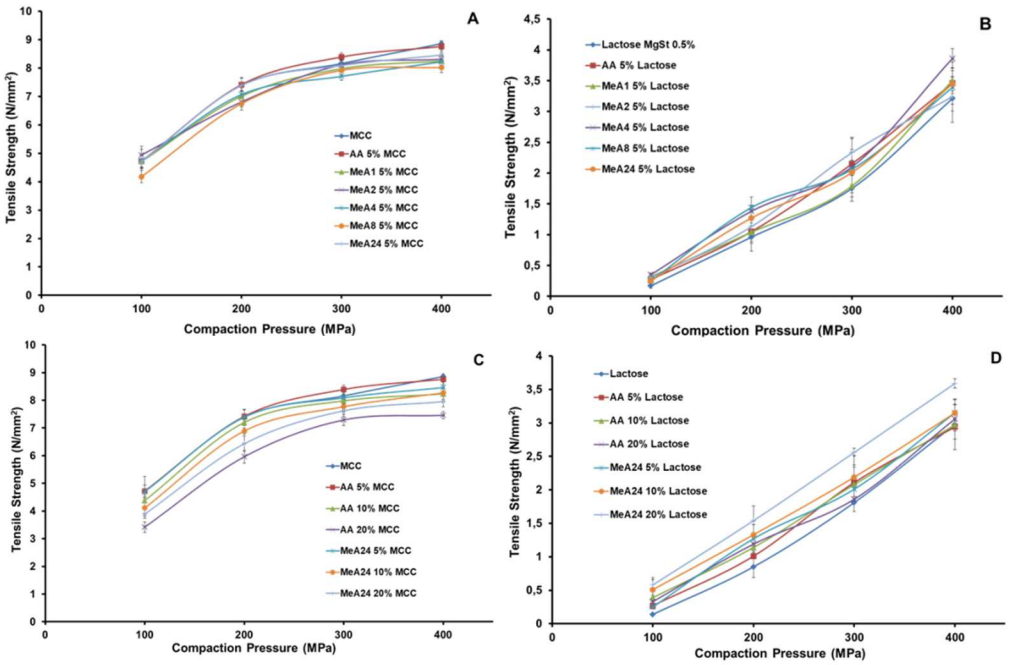

Figure 6. Curves of tensile strength as function of compaction pressure for (A) formulations with MCC and 5% of AA and methylated compounds; (B) formulations with lactose and 5% of AA and methylated compounds; (C) formulations with MCC and 5, 10, 20% of AA and MeA24; (D) formulations with lactose and 5, 10, 20% of AA and MeA24.

Tablets possessing similar tensile strength, 4.2-4.9 N/mm^2 for MCC formulations and 3-3.5 N/mm^2 for lactose were produced to analyze the effect in DT induced by AA and its derivatives. Figure 7A illustrates that the disintegration of the formulated mini-tablets with MCC was largely influenced by the addition of 5% of the materials under study.

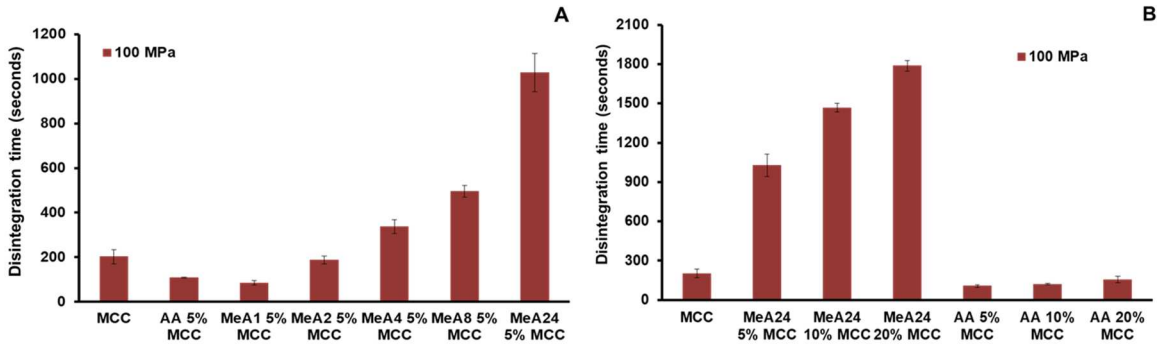

Figure 7. (A) Disintegration times for mini-tablets at 4.2-4.9 N/mm^2 for MCC formulations with (A) 5% AA and methylated derivatives; (B) 10 and 20% AA and MeA24.

In the formulation with MCC, while alginic acid, MeA1 and MeA2 exhibited a rapid disintegration (lower than 3 minutes), higher degrees of methylation reduced gradually the DT of the tablets (environ 6, 8 and 17 minutes for MeA4, MeA8 and MeA24 formulations, respectively). The shorter DT observed for AA and MeA1, compared to pure MCC, can be inferred by the weakening of the tablets structure and by the creation of capillary pores. The combination of these two phenomena allows the water to enter the tablet matrix and then to break the hydrogen bonding between adjacent bundles of formulated particles. As the degree of methylation augments, the character hydrophobic of the modified polysaccharides prevents the water penetration and as a result TD rises (Bladzki et al. 2008).

Due to the differences observed in disintegration times for AA and MeA24 pure tablets, the effect of a higher content presence (10 and 20%) in tablet formulation was also studied. Figure 7B shows how the disintegration time can be readily tuned by the percentage of MeA24 added to the formulation containing MCC. While increasing the amount of MeA24 in the MCC formulations resulted in a considerable increase of the disintegration time (*c.a.* 17, 25 and 30 minutes), for AA this increase was negligible for the preparation of control release oral forms.

All lactose formulations disintegrated faster (less than 1 minute) than pure lactose tablets (environ 4 minutes). For AA this can be explained by a potential synergistically action between the alginic acid which possess the ability to absorb water (wicking action) and the rapid dissolution of crystalline lactose. Lactose has been shown to disintegrated very quickly in water as a result of rapid liquid uptake and fast release of the bonds (Vromans et al. 1987). The hydrophobic effect seen for MCC formulations does not seem to have an effect in the case of lactose. This suggests that the mechanism of disintegration for all tested formulations is led mainly by the rapid dissolution of lactose.

It is important to highlight that this part of the work is only a proof of concept of the potential use of these methylated materials as versatile excipients for the preparation of solid dosage forms. These results show only an example of how this esterification approach can provide a control of the dissolution pattern via modification of the polysaccharide structure. They also open interesting perspectives on the use of these materials in a variety of functionalities such as, disintegrant or filling/binding agent, for the preparation of immediate or sustained release dosage forms. As by all means, different released rates

could be anticipated by adjusting parameters such as degree of methylation, compression force applied, formulation or nature of the API.

4. Conclusion

The effect of the degree of methylation of alginic acid on the physicochemical and compaction properties was thoroughly examined. Modified alginates presented enhanced mechanical properties, tensile strength and compressibility, when compared with native alginic acid powder. Mini-tablets obtained with MeA24 presented high hardness levels, comparable to pure MCC, making this material an interesting candidate for being used as direct compression filler/binder. Also, an improvement of the flowability seems to occur which is currently under study. In addition, these materials showed multifunctional behaviour determined by the degree of methylation, disintegrant or sustained-release, due to the introduced hydrophobicity which extends dissolution times. Overall, this work demonstrated that methyl ester derivatives of alginic acid exhibit very interesting functional properties for the potential development of multifunctional excipients used in direct compression.

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