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1 Development of alginate esters as novel multifunctional excipients for direct compression

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11 Abstract

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

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

25 1. Introduction

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

35 In this framework, alginic acid and its salts, emerge as an excellent choice to develop added-value
36 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.

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

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

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

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

74

75 **2. Materials and Methods**

76 2.1 Materials

77 Methylated alginates were prepared from alginic acid (AA; CAS 9005-32-7; Lot SLBT2973) (Sigma-
78 Aldrich, Germany) with 43% in guluronic acid and presenting an organization in block of their
79 polysaccharides chains. The main characteristics of the alginic acid used in this study were determined
80 by routine ^1H liquid-state NMR analysis and are the following: the respective fraction of mannuronate
81 (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} :
82 0.31); the η parameter, which describes the alternation of M and G groups, is equal to 0.49 which
83 corresponds to a sequenced block-copolymer; the N_G , that represent the average number G units in G-
84 blocks equal to 4. The samples were prepared as described previously by Grasdalen (Grasdalen et al.
85 1979). Sulfuric acid 96% was purchased from Sigma-Aldrich. Distilled water was used for the
86 preparation of all solutions.

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

91 2.2 Preparation of methyl ester alginic acid

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

99 2.3 Physicochemical characterization

100 2.3.1 FTIR

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

106 2.3.2 X-ray Diffraction

107 Powder X-ray diffraction (XRD) patterns were recorded using a Bruker D8 Advance diffractometer and
108 the monochromatic Cu $K\alpha_1$ radiation ($\lambda = 1.5406 \text{ \AA}$, 40 kV and 40 mA). They were recorded with 0.02°
109 (2θ) steps over the 10-80° 2θ angular range with 0.1s counting time per step using LINXEYE detector
110 1D.

111 **2.3.3 Scanning Electron Microscopy**

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

114 **2.3.4 Thermal gravimetric analysis**

115 Composition and thermal behavior were evaluated on 10 to 20 mg samples weighed in a ceramic pan,
116 by Thermal Gravimetric Analysis (TGA, STA 6000, Perkin Elmer) from 30 to 600 °C at a heating rate of
117 15 °C/min under airflow.

118 **2.3.5 ¹³C solid-state NMR**

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

122 **2.3.6 True density**

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

126 **2.4 Compaction study**

127 **2.4.1 Tableability**

128 Pharmaceutical tablets of 25 mg of each material were compressed using a rotary tablet press simulator
129 Styl'One Evolution (using Analis software, Medelpharm, France) at different compaction pressures (100,
130 200, 300 and 400 MPa). Flat punches of 3 mm diameter were used for the compaction study and the
131 speed rate was of 10 tablets/min. Styl'One comprises one compaction station with a system of punch
132 displacement control. The tare of the force sensors was done automatically and the tare of the
133 displacement transducers was performed using the "standard" mode using a gage block of 1 mm, before
134 starting each acquisition.

135 Tablets of 400 mg were compacted at 100, 200 and 300 MPa compaction pressures. Flat punches of
136 11.28 mm diameter were used for the compaction study and the speed rate was of 10 tablets /min.
137 Tablets tensile strength was calculated using hardness, thickness and diameter data measured using a
138 Sotax Multitest 50FT (Sotax AG, Switzerland).

139 The diametric tensile strength (TS) was calculated from the crushing force using the following equation
140 (1):

$$141 \quad TS=2F/\pi Dh \quad (1)$$

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

144 **2.4.2 Compressibility**

145 Compressibility of alginates was evaluated by the measurement of tablet porosity according to equation
146 (2)

$$147 \quad \varepsilon = 1 - \rho r \quad (2)$$

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

$$149 \quad \rho r = \rho T a / \rho T r \quad (3)$$

$$150 \quad \rho r = m T / \pi R^2 h T \rho T r \quad (4)$$

151 Where $\rho T a$ is the density of tablet, $\rho T r$ true density, R the radius of tablet, hT its height and mT its mass.

152 **2.4.3 Heckel and Walker modeling**

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

$$157 \quad \ln\left(\frac{1}{1-D}\right) = KP + A \quad (5)$$

158 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
159 part of the Heckel plot. Hersey and Rees defined that P_y values can be used to characterize the
160 deformation mechanism of materials (Hersay et al. 1971). For them, the low value of P_y reflects the
161 plastic deformation of a hard ductile powder while P_y high value reflects a fragmentary deformation of a
162 brittle material under compaction force. Heckel equation was fitted for all the materials using data
163 collected from in-die compaction experiments. The fitting of the models was performed using regression
164 by minimization of the sum of squared errors. The software Analis (Medelpharm, France) was used for
165 the fitting of the model. Qualitative assessment was made to select the most central part of the linear
166 region. The regression coefficient was then calculated for this selected region.

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

$$170 \quad 100V = -W * \log(p) + C \quad (6)$$

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

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

176 **2.5 Disintegration time *in vitro***

177 A modified disintegration prototype apparatus was developed in house to evaluate the disintegration
178 time (DT) of the mini-tablets produced. The tested tablets were manufactured at similar tensile strength.
179 The design of this device is inspired by the experimental setup previously described which applies a
180 constant force on the tablet during the disintegration (Abdelbary et al. 2005). The tablet is placed on a
181 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
182 distilled water is added onto the filter paper and a stopwatch is started. When the cantilever stops
183 displacement, the disintegration is considered completed and the stopwatch is stopped to record the
184 time. Each test was repeated 5 times and results are expressed as the mean value \pm standard deviation.

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

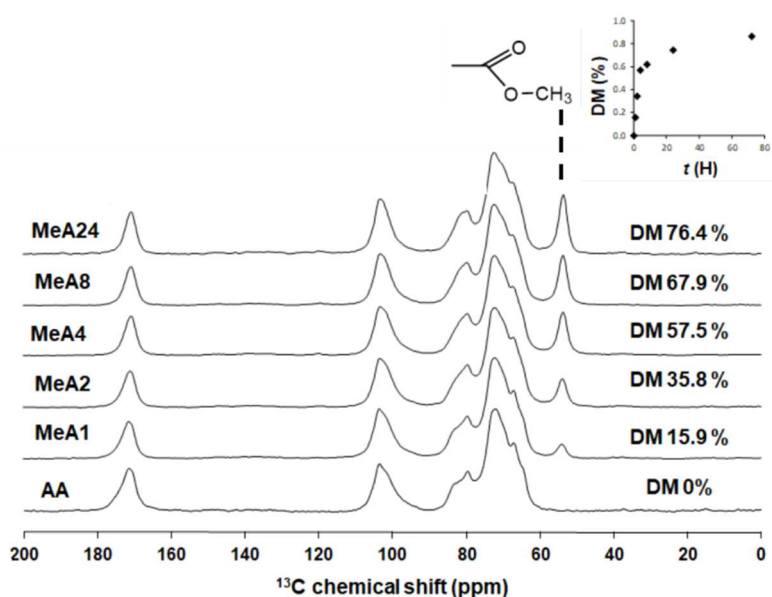
190 **3. Results and discussion**

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

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

202 **3.1 Physico-chemical characterization**

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



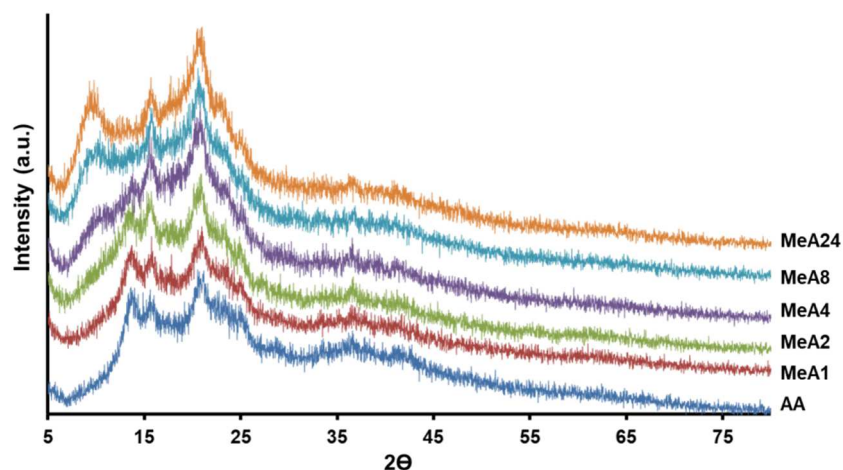
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206 Figure 1. Solid-state $^{13}\text{C}\{^1\text{H}\}$ CP-MAS NMR spectra of alginic acid ($t_c = 1.5$ ms) and methyl alginate
 207 materials ($t_c = 1.0$ ms) obtained at different esterification times., respectively. DM – Degree of
 208 methylation;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

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

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

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



226

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

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

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

236 3.2 Functionality Study

237 3.2.1 Pure powders

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

244 Table 1. Parameters derived from Heckel and Walker models.

Material	P_y (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
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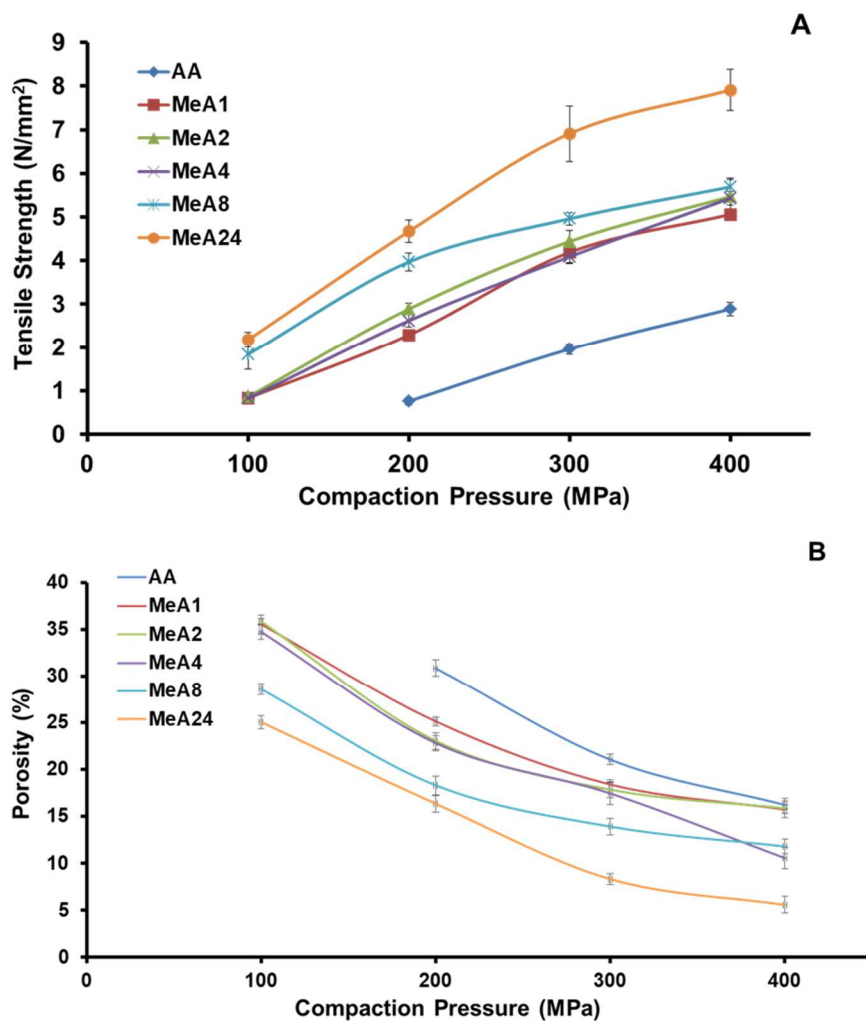
245

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

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

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

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



270

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

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

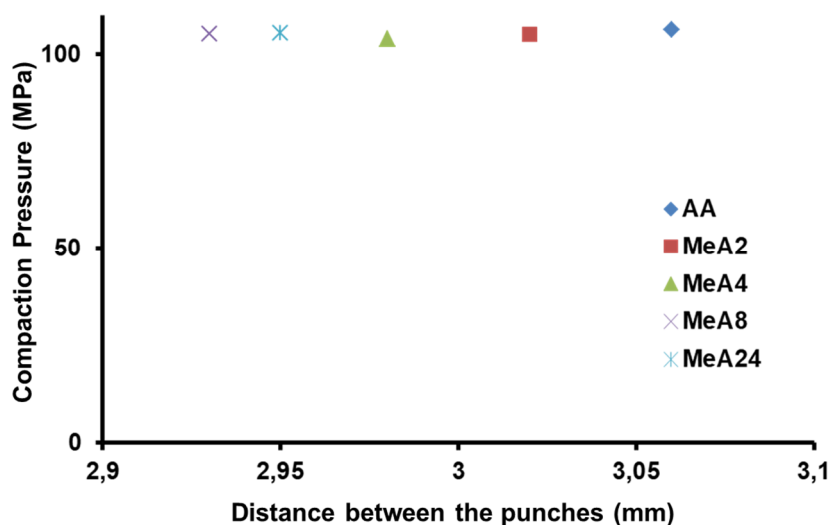
279 This trend was also corroborated by the profiles of compressibility represented by a plot showing the
 280 reduction of tablet porosity with increasing compaction pressure (Figure 3 B). Compressibility is the
 281 ability of a material to undergo a reduction in volume as a result of an applied pressure.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

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

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

297 It should be also pointed out that the fact of producing tablets with high hardness levels, comparable to
 298 pure MCC (8.7 N/mm² at 400 MPa) (Formulation Part), especially for MeA24 (7.9 N/mm² at 400 MPa),
 299 make these materials interesting candidates for being used as direct compression fillers/binders.

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



302

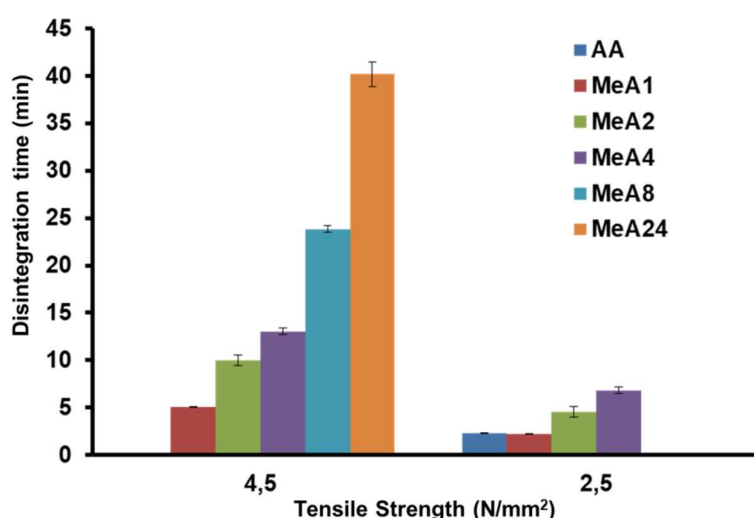
303 Figure 4. Minimum distance between the punches measured for the different powders at comparable
 304 compression force.

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

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

316 3.2.2 Disintegration times

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



321
 322 Figure 5. Disintegration times for mini-tablets at 2.5 and 4.5 N/mm² for AA and methylated derivatives.
 323

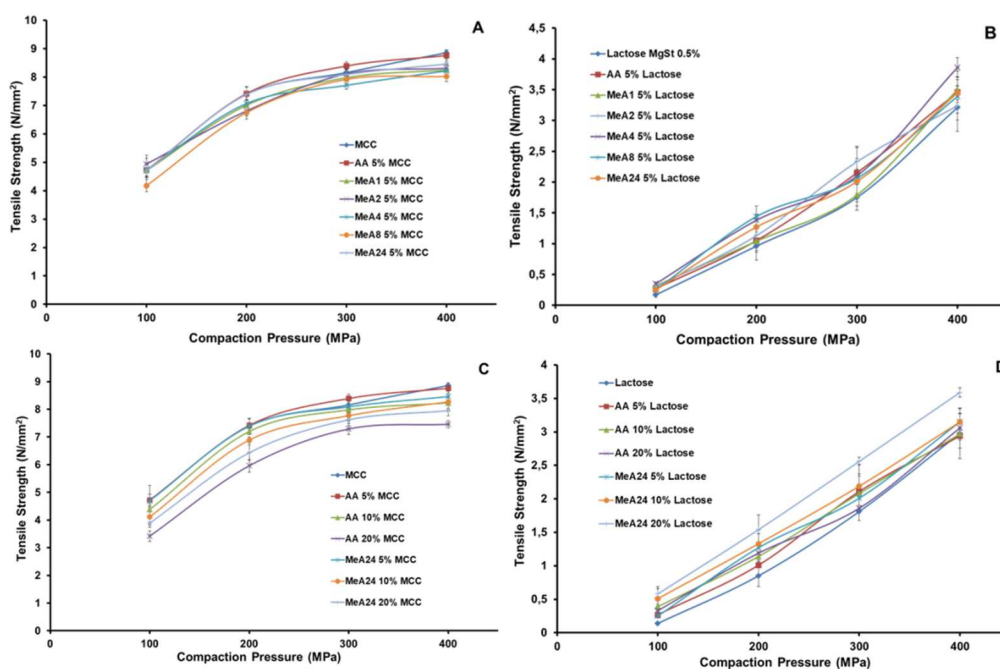
324 It was found that disintegration time increases with the degree of esterification. As the disintegration
 325 time of AA has been found not to be correlated to the swelling force but mainly related to the water
 326 uptake kinetics (Soulaïrol et al. 2018), the higher DT values observed on the modified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

336 3.3 Formulation

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

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

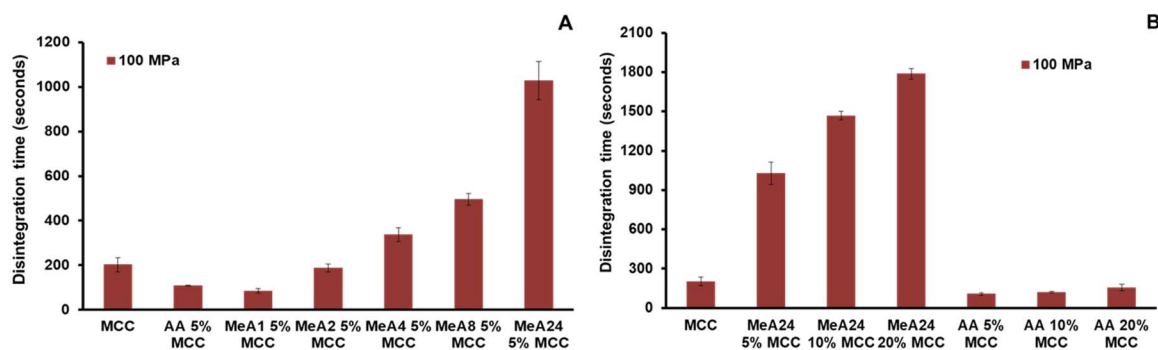
347



348

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

353 Tablets possessing similar tensile strength, 4.2-4.9 N/mm² for MCC formulations and 3-3.5 N/mm² for
 354 lactose were produced to analyze the effect in DT induced by AA and its derivatives. Figure 7A illustrates
 355 that the disintegration of the formulated mini-tablets with MCC was largely influenced by the addition of
 356 5% of the materials under study.



357

358 Figure 7. (A) Disintegration times for mini-tablets at 4.2-4.9 N/mm² for MCC formulations with (A) 5%
 359 AA and methylated derivatives; (B) 10 and 20% AA and MeA24.

360 In the formulation with MCC, while alginate acid, MeA1 and MeA2 exhibited a rapid disintegration (lower
 361 than 3 minutes), higher degrees of methylation reduced gradually the DT of the tablets (environ 6, 8 and
 362 17 minutes for MeA4, MeA8 and MeA24 formulations, respectively). The shorter DT observed for AA
 363 and MeA1, compared to pure MCC, can be inferred by the weakening of the tablets structure and by the
 364 creation of capillary pores. The combination of these two phenomena allows the water to enter the tablet
 365 matrix and then to break the hydrogen bonding between adjacent bundles of formulated particles. As
 366 the degree of methylation augments, the character hydrophobic of the modified polysaccharides
 367 prevents the water penetration and as a result TD rises (Bladzki et al. 2008).

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

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

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

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

389 **4. Conclusion**

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

400

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