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1 *Review*

2 **Sodium alginate and alginic acid as pharmaceutical excipients for tablet formulation:**
3 **Structure-Function Relationship**

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9

10 **Abstract:** Alginic acid and its sodium salt are well-accepted pharmaceutical excipients fulfilling
11 several roles in the development of solid oral dosage forms. Although they have attractive
12 advantages as safety, abundance, relatively low cost and biodegradability, these natural
13 polysaccharides possess a high variability that may limit their use as excipients for tablet formulation.
14 Thus, to obtain robust formulations and high-quality drug products with consistent performance a
15 complete understanding of the structure-property relationship becomes necessary as the structure of
16 alginates affects both, technological and biopharmaceutical properties. This review compiles the
17 compaction studies carried out that relate the structure of alginates to their mechanical and
18 dissolution performances. The different analytical methods used to determine the chemical
19 composition, primary structure and molecular weight distribution, major factors affecting the behavior
20 of alginates in direct compression, are also exposed. Finally, different strategies reported to improve
21 the properties of alginic acid as direct compression excipient are discussed.

22 **Keywords:** sodium alginate, alginic acid, biosourced, pharmaceutical excipient, direct compression,
23 tablet formulations

24

25 **1. Introduction**

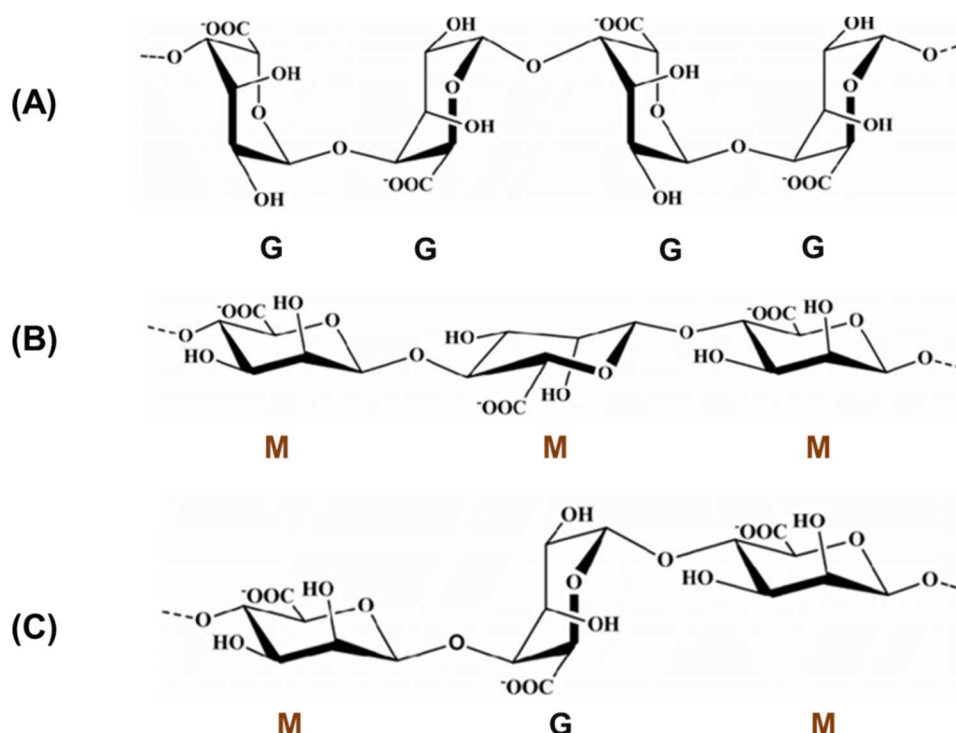
26 The oral route of drug administration is often considered the most convenient for both patients
27 and pharmaceutical industry, with tablets being the most popular solid oral dosage form. Tablets have
28 numerous advantages over other delivery systems such as, ease of administration, high patient
29 compliance and the ability to modify the release of active pharmaceutical ingredients. Besides, from an
30 industrial perspective, tablets are relatively easy to manufacture, require shorter processing times and
31 show good physical and microbiological stabilities (Augsburger & Hoag 2008).

32 Direct compression is generally the preferred mode for tablet manufacturing; in this process, the
33 dry constituents, active ingredients and excipients, are thoroughly mixed and then compressed into
34 tablets. The assets of direct compression are well-known, the most relevant being the reduction in the
35 number of processing steps and the elimination of the effects of heat and moisture.

Abbreviations: AA – Alginic acid; NaA – Sodium alginate; M – β -D-mannuronic ; G – α -L-guluronic
acid; CaA – Calcium alginate; HPMC – Hydroxypropylmethylcellulose; MCC – Cellulose
microcrystalline; MW – Molecular weight; MWD – Molecular weight distribution; SEC – Size exclusion
chromatography; CD – Circular dichroism.

36 The exploration and development of biosourced direct compression excipients is a topic that
 37 continues attracting significant attention in the pharmaceutical excipient market and it is expected to
 38 be worth 8.53 USD billion by 2023 (Research and Markets, 2018). Suitable pharmaceutical excipients
 39 should not only be directly compressible themselves, but also capable of being mixed with a large
 40 proportion of drug substance without significant deterioration in the tablet quality (Jivraj et al. 2000;
 41 Koo 2017). In this regard, natural resource-based polymers such as cellulose, pectins, gums,
 42 mucilages, carageenans or alginates have found great interest as excipients in direct compression due
 43 to their abundance, biodegradability and nontoxicity (Li et al 2014; Thoorens et al. 2014; Rubinstein et
 44 al. 1993; Gupta et al. 2001; Carien et al. 2009; Lin et al. 2019). Each of these polysaccharides
 45 presents unique properties, specific structural characteristics and corresponding functional
 46 performance. Thus, their study would provide further technical versatility and diversify functionality. In
 47 addition, it has been demonstrated that as technology and testing techniques advance, their
 48 physicochemical nature is better understood, allowing them to be adapted to broader pharmaceutical
 49 applications.

50 Alginates are hydrophilic polysaccharide composed of linear copolymers containing blocks of
 51 (1,4)-linked β -D-mannuronic (M) and α -L-guluronic acid (G) residues (Lee & Mooney 2012). The
 52 blocks are composed of consecutive G residues (GGGGGG), consecutive M residues (MMMMMM),
 53 and alternating M and G residues (GMGMGM) (Figure 1). The proportion of the three types of blocks –
 54 MM, GG and MG is going to play a critical role on the physical properties of alginates.



55

56 Figure 1 (a) Homopolymeric blocks of poly- α -1,4-L-guluronic acid (GG); (b) Homopolymeric
 57 blocks of poly- β -1,4-D-mannuronic acid (MM); (c) Heteropolymeric blocks of alternating M and G
 58 residues.

59 Although, these anionic polymers are mainly extracted from brown seaweeds of the following
60 genera *Ascophyllum*, *Durvillaea*, *Ecklonia*, *Laminaria*, *Lessonia*, *Macrocystis* and *Saccharina* seaweed
61 (Andriamanantoanina & Rinaudo 2010; Vauchel et al. 2008; Gomez et al. 2009; Peteiro 2018);
62 alginates can also be extracted from bacterial sources (e.g. *Azotobacter vinelandii*). The main
63 difference at the molecular level between algal and bacterial alginates is the presence of C2 and / or
64 C3 O-acetyl groups in bacterial alginates (Rehm & Valla 1997). Although it is possible to produce
65 alginates with different molecular weights and reproducible physico-chemical characteristics by
66 manipulating the culture conditions during fermentation, the current rate of production only allows the
67 use of bacterial alginate as a biomaterial in the fields of biomedicine and tissue engineering. (Urtuvia
68 et al. 2017) Thus, this review will focus only on work done with alginates extracted from brown
69 seaweeds.

70 Alginates obtained from different algae species, season and place of harvesting will differ
71 significantly in their chemical composition (mannuronic/guluronic (M/G) ratio), structural/block
72 organization, and physicochemical properties (molecular weight, rheological characteristics, moisture
73 content, particle size distribution, purity, etc.). The extraction method and process parameters
74 (temperature, time of extraction, alkali concentration and pre-treatment) have also shown an impact on
75 the properties of the produced alginate (Vauchel et al. 2008; Chee et al. 2011). For instance,
76 alginates' rheological properties have been found to be greatly dependent on the processing
77 temperature (Vauchel et al. 2008). Thus, although an increase of the treatment temperature can
78 improve the extraction yield, a decrease of viscosity was also observed (Hernandez-Carmona et al.
79 2013). The molecular weight (MW) can also differ depending on the extraction method used (Borzajani
80 et al. 2017). In a study reported by Gomez *et al.*, three routes of precipitation of sodium alginate from
81 *Macrocystis pyrifera* using ethanol, HCl or CaCl₂ were compared. Analysis of the different products
82 showed that while the ethanol route had the lowest number of steps and displayed the best
83 performance; the CaCl₂ route gave alginates with the lowest MW and poorer mechanical properties
84 (Gomez et al. 2009). Moreover, since alginates are obtained from a natural source, a variety of
85 impurities such as heavy metals, proteins and endotoxins may potentially be present. For applications
86 in the food and beverage industry, low levels of these impurities are not a problem, but for
87 pharmaceutical applications and in particular, when the alginate is used in parenteral administration,
88 these impurities must be removed (Gombotz & Wee 1998). In view of this, limits not to be exceeded
89 are recommended in the European Pharmacopeia for sodium alginate (NaA) and alginic acid (AA)
90 (European Pharmacopeia 2017).

91 Traditionally alginates have been used in the food and cosmetic industries as thickening or
92 viscosity increasing agents (Ruocco et al. 2016; Kontominas 2020; Yao et al. 2018; Solah et al. 2010).
93 In a pharmaceutical context, while AA has been used mainly as disintegrant in compressed tablets
94 designed for immediate release (Onsøyen 1996; Shotton & Leonard 1976); sodium alginate has
95 fulfilled several roles such as suspending agent, tablet binder, taste masker, controlled-release matrix
96 or elastically deforming excipient in soft tableting, approach used to improve the performance of
97 pressure-sensitive drugs (Szekalska et al. 2016; Kaneko et al. 1997; Gomez D'Ayala et al. 2008;
98 Tonnesen & Karslen 2002; Schmid & Picker-Freyer 2009).

99 As certain alginate's properties can be related to its functionality and mechanical performance,
100 the selection of a specific type or grade of this excipient can affect the performance of the formulated
101 product (Rioux et al. 2007; Moreton 2009). For example, pH dependence has been observed in
102 alginate-based matrix tablets determined by their monomer content; while tablets containing M-rich
103 alginates gave higher chlorpheniramine maleate and metronidazole release in phosphate buffer, G-
104 rich alginates gave higher drug release rates in acidic media (Liew et al. 2006; Sriamornsak et al.
105 2007). Thus, in order to successfully achieve the desired therapeutic performance, evaluation and
106 understanding of the alginate's physicochemical properties at the molecular and particulate level prior
107 to tablet processing becomes fundamental.

108 The literature mainly describes three different methods for determining the composition and
109 structure of alginates: chemical, enzymatic and physicochemical methods (Usov 1999). As chemical
110 methods are typically based on acidic hydrolysis of glycosidic bonds which can lead to partial
111 degradation of the monosaccharides liberated; and enzymatic treatment leads principally to a mixture
112 of oligomers with low degrees of polymerization which can be of special interest for the production of
113 oligo-alginates with potential applications in therapeutics and in biotechnology (Courtois 2009;
114 Iwamoto et al. 2005). Only physicochemical characterization methods will be examined in this review
115 because, in our opinion, they are more suitable to be introduced in an industrial pharmaceutical
116 context, as they can be used in- or at-line in continuous manufacturing processes; they are also faster
117 and allow the analysis of small amounts of raw material.

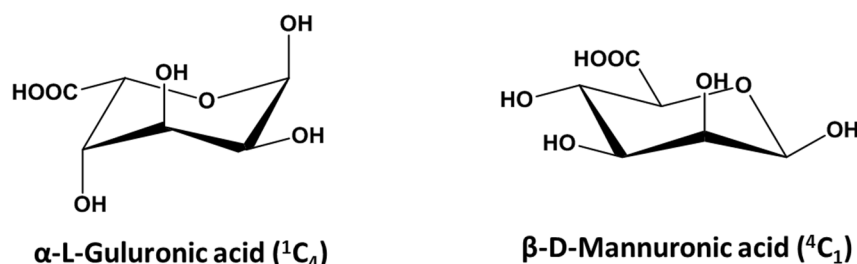
118 Therefore, in this article, we have reviewed studies that collect information regarding the use of
119 AA and NaA as excipients for direct compression. This review exposes that due to the great variability
120 of natural materials such as alginates, a good determination of their physicochemical properties would
121 be crucial in order to establish reliable structure-functionality relationships. With this aim, the different
122 analytical methods used for the determination of the composition, primary structure and MW of
123 alginates, major factors affecting the behavior of alginates in direct compression, are exposed,
124 followed by the different compaction studies carried out that relate the structure of alginates to their
125 mechanical and dissolution performances. The analyzed information will provide a clear prospect of
126 the additional studies that will still be needed to fully exploit the capabilities of alginates as
127 pharmaceutical excipients for direct compression.

128 **2. Structure of alginates**

129 Alginate is an unbranched block copolymer composed of homopolymeric β -D-mannuronate M
130 and α -L-guluronate G blocks, which have no regular repeating units. The proportion and arrangement
131 of these uronic blocks provides unique physicochemical properties to the alginates and vary, as
132 mention above, to a large extent depending on their source and extraction method (BeMiller 1999).

133 X-ray diffraction studies of mannuronate-rich and guluronate-rich alginates have been performed
134 to gain knowledge on the conformation of the monomer rings. Results shown that guluronate residues
135 in the homopolymeric blocks were in the 1C_4 conformation, while the mannuronate residues were in
136 the 4C_1 conformation (Figure 2) (Draget et al. 2005; Ertesvåg et al. 1995; Grasdalen et al. 1977).

137 Therefore, alginate contains all four possible glycosidic bonds: diequatorial (MM), diaxial (GG), axial
 138 equatorial (MG) and axial-equatorial (GM). This difference in the stereochemistry of mannuronic and
 139 guluronic acid monomers is expected to affect the flexibility of alginate chains depending on the M/G
 140 composition and the sequence of the chain.



141

142

Figure 2. Conformational structure of alginate monomers.

143 X-ray patterns also showed that AA and alginate salts possess an amorphous structure with
 144 some extend of higher structural order. The presence of two diffraction peaks at 16 and 21° indicates
 145 certain order due to the presence of homopolymeric blocks (MM or GG) in the molecular chain of AA
 146 (Ikeda et al. 2000).

147 One of the most exploited physical properties of alginates is their capability to form gels by
 148 selective binding multivalent cations or by acid precipitation. Unlike other polysaccharides such as
 149 gelatine and agar, the sol/gel transition of alginates is not particularly influenced by temperature
 150 (Skjåk-Bræk & Draget 2012). Although calcium-alginate gel is extensively used in pharmaceutical and
 151 medical applications such as wound dressings, enzyme immobilization or control-release drug delivery
 152 systems (Kontominas 2020; Kothale et al. 2020). This alginate salt is much less used as excipient for
 153 the preparation of tablets by direct compression and is therefore not covered in this review.

154 The association of alginates' chains and the gel structure and mechanics, depends not only on
 155 the ion type, but also on the sequence and composition of the alginate chain that determines the
 156 stiffness. Therefore, the total content of α -L-guluronic acids and more precisely, the relative length of
 157 G-blocks are important criteria for the ability of alginates to form gels (Stokke et al. 2000). In this
 158 manner, while a high proportion of GG blocks have been reported to lead to a rigid and brittle gel, MM
 159 blocks induced the formation of soft and elastic gels and the presence of MG blocks gave them
 160 flexibility (Draget et al. 2000). These observations have been corroborated by bond-angle correlation
 161 function calculus on the stiffness of NaA blocks (Hecht & Srebnik 2017; 2016). Results showed that
 162 characterizing the flexibility of alginate chains is challenging as it exists a complex dependence
 163 between chain flexibility/gelation properties and monomer sequence, alginate concentration, type of
 164 counterion, ionic strength and sample polydispersity (Liling et al. 2016; Baños et al. 2014). As an
 165 example of this complexity, different interchain association mechanisms, such as lateral association,
 166 zipper mechanism and entanglement can be observed just by changing the guluronic content in the
 167 NaA chain.

168 In order to gain a better molecular understanding of the physical properties of alginates in solution
 169 and in gel state, researchers have used Mannuronan C5-epimerases (AlgE4) to tailor alginates into a
 170 more defined structures, as well as into extreme compositions with narrower compositional distribution
 171 than those occurring in nature. These sequences, which exhibit a less variable nature, should be

172 useful for establishing structure-properties relationships without the need of statistical assumptions
173 and thus provide a better molecular understanding of the properties of the alginate molecule as a
174 whole (Draget et al. 2000). For instance, the increased acid solubility of alternating sequences
175 introduced by the action of AlgE4 in AA gel formation was explained by increased conformational
176 entropy of the less extended epimerized chains and a lack of intermolecular cross-linking between the
177 alternating sequences.

178 As the structure of alginates affects not only their gelling properties and drug delivery behaviour,
179 but also their mechanical properties in powder form (Sanchez-Ballester et al. 2020); detailed
180 characterization of these materials will be necessary to fully understand the relationship that exists
181 between alginates' structure and their functionality.

182 **3. Analytical methods used for the characterization of alginic acid and alginates salts**

183 As many different grades of NaA are commercially available from manufacturers, it becomes
184 essential to be aware of how differences between alginates can affect the performance parameters of
185 pharmaceutical formulations. To this end, researchers have developed various techniques that allow
186 the determination of alginates' composition, uronate residue arrangement and MW in a fast, precise
187 and simple manner.

188 **3.1 Determination of the composition and primary structure**

189 Historically, the determination of monomer content of alginic acids and their alginate salts was
190 performed by complete hydrolysis of the glycosidic bonds followed by separation techniques such as
191 paper chromatography, thin layer chromatography, anion-exchange liquid chromatography, and gas-
192 liquid chromatography (Usov 1999). Important drawbacks of these methods were that complete
193 hydrolysis destroyed the sequence distribution and substantial errors were made when attempting to
194 determine the relative composition. But these studies also brought important findings such as: the G
195 blocks appear to be more resistant to hydrolysis than the M blocks (Ikeda et al. 2000). And that the
196 specific loss of each monomer by hydrolysis seems to depend on the pattern of their block distribution
197 within the polymeric molecule. Therefore, it was concluded that the selection of versatile conditions for
198 hydrolysis is quite challenging as the destruction of monomers makes the final determination of the
199 composition differ considerably in ratios and distribution of uronic acid residues from their primary
200 structure.

201 Nowadays, the most common and reliable method used for the structural analysis of alginates is
202 ^1H and ^{13}C solution-state NMR spectroscopy (Grasdalen et al. 1977; Penman & Sanderson 1972;
203 Grasdalen et al. 1979; 1983; 1981). This method is rapid and particularly useful for quantitative
204 analysis in cases where only small amounts of sample are available. In addition, only slight controlled
205 depolymerisation of the alginates before analysis is required to eliminate the problem of viscosity,
206 which is much more favourable than the heterogeneous, total hydrolysis used in the past for the
207 determination of the M/G ratio (Haug et al. 1966; 1967).

208 ^{13}C NMR was for the first time used on alginates to determine the monomer sequence by using
209 the doublet and triplet frequencies (Grasdalen et al. 1977). It was found that multiplets recorded at 25
210 MHz reflected the sequence of units and the signals for the anomeric carbons were sensitive to the

211 nature of the neighbouring unit (M or G). The mannuronate (M)/guluronate (G) molar ratio and relative
212 content of pairs of monomers (MM, MG, GM and GG) was the first time obtained from the intensities of
213 the signals for the anomeric protons (Grasdalen et al. 1977; 1979). On the other hand, while the
214 relative content of triplets with a central M (MMM, GMG, GMM and MMG) was determined in this
215 pioneering study; the number of triplets with central G residue were not found. The content of each
216 type of triplets in several specimens of alginates samples was reported a few years later a higher-
217 resolution NMR spectrometer (50 MHz) (Grasdalen et al. 1981). Further developments of the ^1H NMR
218 method allowed the study of the composition and the sequence of urinate residues in intact alginates
219 by using high-field 400 MHz NMR equipment (Grasdalen 1983). This study provided information about
220 guluronated-centred triads previously accessible only from high field ^{13}C NMR spectroscopy and
221 supported some predictions about linkage conformations previously obtained by hard-sphere
222 calculations (Grasdalen et al. 1981; Whittington 1971).

223 More recently, solid-state NMR (SSNMR) spectroscopy has been used as an alternative tool to
224 solution-state NMR for characterization of NaA powders. The main advantage of this technique is that
225 partial acid hydrolysis of high-molecular-weight alginates prior measurements is not required
226 (Salomonsen et al. 2009; 2009). It is worth mentioning that while in solution ^{13}C NMR eight distinct
227 signals corresponding to the chemical shift values of specific G or M residues are clearly observed in
228 the spectra; the SSNMR spectra showed only five distinct peaks for these carbons due to the broad
229 and overlapping signals typical of amorphous materials. This fact increases the difficulty of finding a
230 specific peak in SSNMR compared to liquid state spectra. One way to successfully improve signal
231 resolution was to use hydrated alginates (Sperger et al. 2011). This simple strategy resulted in more
232 obvious differences in the spectra for the pyranose ring carbon signals in the 60-90 ppm region.
233 Furthermore, a correlation between the relaxation times of the NaA samples with similar chemical and
234 water content and the intrinsic viscosity and thus MW was also found. It is also worth mentioning that
235 SSNMR has been described as sufficiently sensitive and selective to monitor changes in the relaxation
236 time of alginate that has been diluted with another excipient and compressed into tablets.

237 Other analytical methods such as FTIR have been also used to estimate the composition of
238 alginates. The main interest of these methods is also the lack of the previous acid hydrolysis step.
239 Semi-quantitative determination of the M/G ratio using FTIR was firstly developed using G- and M-rich
240 NaA by measuring the ratio of absorption band intensities at 808 (M) and 787 cm^{-1} (G) of specially
241 prepared films (Mackie 1971). Comparison of the intensities of the bands at 1320 (M) and 1290 cm^{-1}
242 (G) has also been found effective for this purpose (Filippov & Kohn 1974). However, factors such as
243 variable moisture content can lead to poor precision and interferences. To address this problematic,
244 Sakugawa *et al.* reported a simplified FTIR method using calcium and manganese alginate salts to
245 restrict the mobility of polysaccharide molecules by fixing them in an "egg-box" structure. But, although
246 this strategy resulted in sharper peaks of polyguluronate compared to those of polyguluronic acid or
247 sodium polyguluronate, the spectra of polymannuronic acid and polymannuronates were nearly
248 identical (Sukugawa et al. 2004).

249 Circular dichroism (CD) has been also used to determine the M/G ratio as the three types of
250 blocks present in alginate molecules differ essentially in their CD spectra. The interest of this

251 technique is that it was possible to determine the composition even for milligram quantities of sample
252 without destruction of the polymer. Furthermore, since the CD spectra of mixed blocks (poly-MG) are
253 not identical the determination of the block composition from their CD spectra is also possible (Morris
254 et al. 1980).

255 Finally, an improved method combining IR, Raman, near infrared (NIR) spectroscopy and
256 chemometrics for a reliable and rapid determination of the M/G ratio was reported by Salomonsen *et*
257 *al.* The M/G values were predicted with an error comparable to that of the solution-state ¹H NMR
258 reference method (Solomonsen et al. 2008). Spectral pre-processing was applied to remove effects
259 not related to the chemical composition of the samples. These results represent a valuable
260 achievement, since vibrational spectroscopic techniques have strong industrial potential for at- or on-
261 line quality control at screening large number of samples.

262 **3.2 Determination of Molecular Weight and Molecular weight distribution**

263 Since the physical properties of alginate gels, such as viscosity, depend in part on their MW; an
264 accurate determination of the MW will be crucial to control the release profile of the tablet actives.
265 Furthermore, as will be explained later in this review, the MW has been proven to have an effect not
266 only on the release profile but also on the mechanical properties of the resulting tablets (Benabbas et
267 al. 2020).

268 Although techniques such as integrated laser light scattering (LLS) at both, wide and low angle
269 has been also shown suitable for the determination of the MW and molecular weight distribution
270 (MWD) of NaA presenting different composition (Martinsen et al. 1991). In general, chromatographic
271 techniques are the most common methods used for the determination of MW and MWD of alginates.
272 High-performance size exclusion chromatography with multi-angle laser light scattering detection
273 (HPSEC-MALLS) was used for characterizing MWD of a range of commercial alginates used as ice
274 cream stabilizers presenting different M/G ratio and monomer sequence distribution. Molecular weight
275 averages were found to vary between 115 000 and 321 700 g/mol and polydispersity indexes (PDI)
276 varied from 1.53 to 3.25 (Tuquois & Gloria 2000). Furthermore, polysaccharide identification can be
277 achieved by high performance HPSEC with the appropriate standard (Rioux et al. 2007).

278 Also, size exclusion chromatography (SEC) was used to determine the degree of
279 depolymerisation of three low-molecular AA samples prepared by acid hydrolysis using phosphoric
280 acid. Number average molecular weight and average molecular weight were calculated also using
281 SEC using a polyacrylic-based polymer as standard. In general, it was observed that MW of all
282 fractions decreased with increase of hydrolyzation time. Also interesting to note that some fractions
283 presented similar MW, although their solubility's in water was different. These differences in solubility
284 were explained by the distinctive sequential structures of these fractions (Ikeda et al. 2000).

285 **4. The influence of the physicochemical properties of sodium alginate on its functionality as** 286 **an excipient for direct compression**

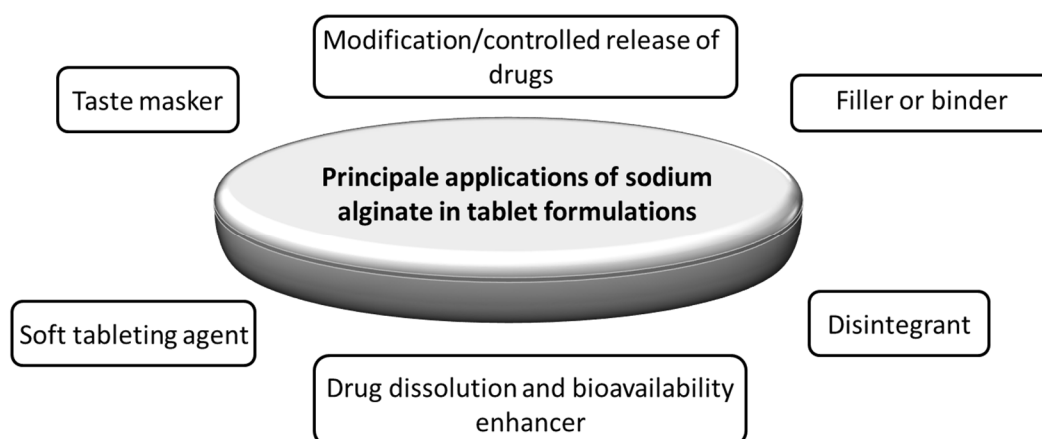
287 Different parameters such as concentration in the tablet formulation, particle size, polymer chain
288 composition, viscosity and MW have been found to be directly related to excipients' tableting
289 properties and drug release profile (Schmid & Picker-Freyer 2009; Liew et al. 2006; Sriamornsak et al.
290 2007). Interestingly, while most of these factors have been largely studied for NaA, very few have

291 been studied for AA. It is also important to note that while these relationships have been widely
 292 explored for alginate hydrogels and salt solutions; little attention has been paid to the impact of these
 293 physicochemical properties in powders.

294 **4.1 Sodium alginate as direct compression excipient**

295 Due to advances in drug delivery technology, it exist the interest of finding excipients which can
 296 be included in novel dosage forms to fulfil specific functions and in some cases even influence directly
 297 or indirectly the extent and/or rate of drug release and absorption. Hence, even if other pharmaceutical
 298 excipients such as hydroxypropylmethylcellulose (HPMC) can find similar applications than sodium
 299 alginate as hydrophilic matrices for drug delivery, their different structure can has an effect on their
 300 mechanical and biopharmaceutical properties. For example, alginates have been described as more
 301 appropriate for tableting pressure sensitive materials than more plastic cellulose derivative materials
 302 as less damage on the pellets was observed using elastic alginates. (Schmid, 2009) Also, more plastic
 303 polymers were proven to be more sensitive to lubricant which can lead to a loss of compressibility.
 304 (Khatri, P. et al. 2018).

305 As Figure 3 summarizes, NaA has an enormous potential as excipient in tablet formulations
 306 fulfilling different roles. The effect of NaA on tablets properties have been found dependent of the
 307 amount incorporated in the formulation. Thus, NaA can promote disintegration when added at a
 308 concentration of 2-10% of the tablet weight or act as a binder/diluent when added at higher
 309 concentrations (Sakr et al. 1978; Veski & Marvola 1993). Sodium alginate has also been extensively
 310 used in the preparation of oral sustained release formulations, as it can delay the dissolution of the
 311 active ingredient from tablets, capsules and aqueous suspensions (Mandal et al. 2009; Holte et al.
 312 2003; Veski et al. 1994; Sanchez-Ballester et al. 2019); or used as taste masker and as elastically
 313 deforming excipient in soft tableting (Szekalska et al. 2016; Kaneko et al. 1997; Tonnesen & Karslen
 314 2002; Schmid & Picker-Freyer 2009). Alginate matrices have been also used for the encapsulation of
 315 proteins and amorphous drugs improving their physicochemical properties (Stender et al. 2018;
 316 Nazemi et al. 2020).



317

318 Figure 3. Overview of the main roles of sodium alginate in the formulation of solid oral tablets.

319 4.2 Sodium alginate structure - tablet compression properties relationship

320 The tableting properties of NaA has been described to be mainly affected by its inherent
321 deformation behavior tightly related to its primary structure/composition and by physical factors such
322 as its particle shape, size, porosity, density and surface roughness.

323 The effect of different M/G ratios on the compaction properties of NaA soft tablets have been
324 investigated by Schmid *et al.* The effect of the particle size was excluded from this study as all
325 substances tested presented a similar particle size distribution (38-48 μm) (Schmid & Picker-Freyer
326 2009). Although particle sizes below 100 μm generally result in poor flowability and low bulk densities,
327 the particle size of the alginates used in this study is comparable to that of Avicel PH 101,
328 microcrystalline cellulose widely used for direct compression tableting. In general, all alginates tested
329 deformed elastically, but tablets containing alginates with low guluronic acid content exhibited greater
330 elasticity than tablets obtained from alginates with low mannuronic acid content. This publication also
331 highlighted that the guluronic acid ratio affected not only the tableting properties but also the behavior
332 of the tablet after storage. Sodium alginate tablets with high guluronic acid content (65-75%) showed
333 higher elastic recovery than low G content alginates (35-45%) after ten days of storage. Also, a trend
334 was observed between the deformation mechanism of alginates and crushing forces. In general,
335 alginates deforming more plastically produced tablets with higher crushing forces. However, this order
336 was not followed by a NaA containing a low G% (35-45 %) and a MW of 180-250 000 g/mol.
337 Interestingly, this alginate gave tablets with the highest crush strength even though it exhibited low
338 plasticity.

339 The MW has been also proven to affect the compaction properties of NaA in the preparation of
340 soft tablets (Schmid & Picker-Freyer 2009). Three NaA with different MW were used in this study (low
341 180-250 000; intermediate 270-325 000 and high 340-400 000 g/mol). For high densification it was
342 reported that NaA presenting a higher MW (270-325 000 g/mol) exhibited higher elastic recovery than
343 NaA with lower MW (180-250 000 g/mol). For lower densifications, the NaA with a higher degree of
344 polymerization (DP) deformed more elastically than the NaA with lower DP. Elastic recovery was
345 calculated using the Armstrong and Haines-Hutt equation, which uses the difference between the
346 minimum tablet height under load and the tablet height after ten days of storage (storage conditions
347 not specified).

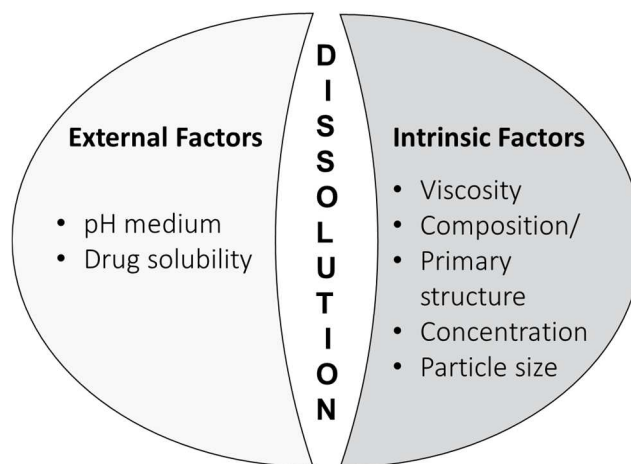
348 Differences in the shape of the alginate particles can also affect the hardness of tablets prepared
349 by direct compression (Moreton 2009). For example, alginates presenting a fibrous form have been
350 described to provide tablets possessing superior hardness due to the potential mechanical interlocking
351 of fibrous and irregularly shaped particles, as previously described in the literature for the case of
352 hydroxypropyl methylcellulose particles (Gustafsson *et al.* 1999). Although excipient particle size has
353 been proven to affect the hardness of tablets for other natural polysaccharides (Velasco *et al.* 1999);
354 there are still no reports explaining its effect on the mechanical properties of the tablets produced with
355 alginates.

356 As these studies demonstrate, the understanding of the tableting properties of NaA is not yet fully
 357 completed. For instance, further studies would need to be realized on the influence of physical
 358 parameters such as particle size on its compression characteristics. In addition, the investigation of the
 359 hierarchical effect of different factors will be essential to develop specifications that will allow users to
 360 employ alginate as excipient in direct compression without unexpected problems due to its natural
 361 variability.

362 4.3 Factors affecting the biopharmaceutical properties of sodium alginate tablets

363 Drug release from hydrophilic NaA matrix tablets is controlled by the formation of a hydrated
 364 viscous layer around the tablet, which acts as a barrier to drug release by opposing the penetration of
 365 water into the tablet, and also the movement of dissolved solutes out of the matrix. Thus, drug release
 366 will be primarily modulated by the diffusion of dissolved drug molecules across the gel layer for water-
 367 soluble drugs, and predominantly by dissolution/erosion mechanism for poorly water-soluble drugs
 368 (Takka & Acarturk 1998).

369 The dissolution of NaA tablets has been reported to be controlled by external factors such as the
 370 pH of the medium; and intrinsic factors such as alginate's viscosity, composition/primary structure,
 371 concentration and particle size (Figure 4) (Hodsdon et al. 1995; Miyazaki et al. 1995; Haug et al.
 372 1967).



373

374 Figure 4. Factors affecting the biopharmaceutical properties of sodium alginate tablets.

375 Alginate matrices show a higher ability to swell in neutral medium (phosphate buffer at pH 6.8-
 376 7.2) than in acidic medium. When NaA matrix tablets are hydrated in acidic conditions (pH < 3), the
 377 outer hydrated surface layer formed around the tablets could be seen visually to possess a very
 378 different consistency than that formed around NaA tablets that have been hydrated in a neutral
 379 medium. The layer formed in acidic medium is not viscous and adhesive in nature, but rather hard and
 380 rubbery in texture. This is probably due to the rapid conversion of NaA to AA (pKa of AA 3.4-4.4) at pH
 381 1-2, which has the ability to swell upon hydration but is essentially insoluble. Therefore, changes in pH
 382 from 6.8 to 1.2 influence polymer hydration and alginate gel rheology due to the ready interconversion

383 of carboxylate anions (NaA) to free carboxyl groups (AA) as the concentration of hydrogen ions
384 increases (Hodsdon et al. 1995).

385 Viscosities of alginates solutions are mainly controlled by their concentration, MW, composition
386 and the arrangement of the mannuronic and guluronic monomer units in the alginate chain (Gombotz
387 & Wee 1998; Holte et al. 2003).

388 Several authors have reported that drug release time is not influenced by the MW of alginates at
389 acidic pH (Efentakis & Buckton 2002; Imai et al. 2000). However, at pH 6.8, alginates presenting
390 higher MW, and thus greater viscosity, resulted in slower release of active ingredients such as
391 furosemide or theophylline than formulations prepared with low and medium viscosity grades that
392 showed the fastest and intermediate release rates, respectively (Efentakis & Buckton 2002; Efentakis
393 & Koutlis 2001). Similar results were obtained by Chan et al. when studying the hydration mechanism
394 and drug release behaviour of compacts prepared from NaA of different MW (Chan et al. 2007). The
395 alginate matrices showed pH-dependent swelling and erosion behaviour, resulting in pH-dependent
396 drug release mechanisms. In its soluble ionic form, while an increase in swelling was observed for
397 alginates with a higher MW, the rate of erosion of the hydrated layer increased for alginates with a
398 lower MW. This particularity allows the use of different viscosity grade alginates to achieve the desired
399 release profile in the buffer phase without changing the release profile in acid.

400 The dissolution profile has been also demonstrated to be influenced by the concentration of
401 alginate used in the tablet. In general, it was found that the time to release 25 and 75% of the drug
402 (T25% and T75%, respectively) increased when the alginate concentration was increased from 10 to
403 30% (Liew et al. 2006; Klaudianos 1972). The lower release times obtained for the 10% alginate
404 matrices were attributed to the formation of a less efficient diffusion barrier due to fewer polymer
405 particles available for the formation of a continuous and resistant gel barrier. In contrast, higher
406 polymer concentrations resulted in a more effective diffusion barrier responsible of the higher values of
407 T25% and T75%. The effect of polymer concentration on drug release had been extensively reported
408 for HPMC matrices (Rekhi et al. 1999; Sung et al. 1996). This effect was justified by an increase in
409 polymer content resulted in an increased viscosity of the gel matrix, causing a reduction in the
410 effective diffusion coefficient of the drug. But given the complexity of swellable matrices, it is unlikely
411 that a change in diffusion coefficient is entirely responsible for the change in drug release rate. Other
412 factors, such as differences in water penetration rate, water absorption capacity and swelling, which
413 result from changes in polymer content, could also play a part in modulating drug release (Skoug et al.
414 1993).

415 Regarding the influence of M/G alginate content, while alginate matrix pellets made from a high
416 guluronic acid content have shown a tendency to form stiffer and more brittle gels; more elastic gels
417 were produced from alginates with low guluronic acid content (Martinsen et al. 1989). Furthermore,
418 alginate pellets containing a guluronic acid content greater than 70% and an average length of
419 guluronic blocks higher than 15 were reported to exhibit less shrinkage, good mechanical strength,
420 better stability and greater porosity that may facilitate drug release.

421 The effect of the M/G content on the dissolution and drug release properties of NaA tablets was
422 also studied by Liew *et al.* In this study different grades of NaA with different M/G content but similar
423 median particle sizes and viscosities were compared (Liew et al. 2006; Klaudianos 1972). It was found
424 that M/G content influenced drug release behavior of alginate matrices only at 30 and 50% alginate
425 concentration. Furthermore, it was found that the pH affected the drug release of alginates presenting
426 different M/G content. Results showed that M-rich alginates gave lower drug release rates in acid
427 medium while G-rich alginates gave lower drug release rates in buffer. It appeared that M-rich
428 alginates hydrated faster under acidic conditions and built up a diffusion barrier more rapidly, resulting
429 in a slower release. At near-neutral pH, G-rich alginates formed more rigid gels upon hydration than
430 M-rich alginates (Veski & Marvola 1993), which may be less prone to erosion and thus constitute a
431 more effective barrier to drug release. The observation in the buffer phase is in agreement with other
432 researchers' findings where pH 7.2 buffer systems were used for the dissolution studies (Veski &
433 Marvola 1993; Efentakis & Buckton 2002).

434 A correlation between the solubility of the alginate under acidic conditions and their composition
435 was found by Haug *et al.* when studying the high solubility of *A. nodosum* stipe (Haug et al. 1967). The
436 observed solubility was attributed to the fact that alginate extracted from this algal species contains
437 mainly alternative mannuronic-guluronic acid residues and therefore a smaller proportion of
438 homopolymer blocks, even when presenting high MW. Thus, the dissolution properties of alginates are
439 determined by both, the proportion between the two monomers and by the sequence of the two
440 monomers along the polymer chain. These findings offer useful insight into how the performance of
441 oral forms produced from different types of alginate can be tailored to specific intestinal-targeted
442 delivery vehicles (Gómez-Mascaraque et al. 2019).

443 The release properties of alginate-containing matrix tablets have been found not only to be
444 affected by the chemical composition but also by the particle size of the powders and the compaction
445 pressure used for their preparation (Liew et al. 2006; Klaudianos 1972). The influence of the particle
446 size on the drug release from other hydrophilic matrices such as HPMC has also been documented
447 (Heng et al. 2001). But unlike HPMC in the case of NaA, analysis of 17 different grades showed that
448 particle size could only be correlated with the dissolution parameters at 10% NaA concentration in the
449 tablet matrix. In general, it was found that as the particle size decreased, the time taken to achieve 25
450 and 75% of chlorpheniramine maleate release increased. However, the relationship between particle
451 size and drug release was not strongly linear and dissolution times were levelled-off at particle size
452 around 100 μm . For the same amount of alginate, a reduction in particle size is accompanied by an
453 increase in the number of particles and an enhancement in the polymer surface area. Hence, the use
454 of smaller alginate particles would favor interparticulate contact, contributing to better polymer particle
455 coalescence and create a less permeable gel barrier for more effective sustained action of drug
456 release. On the other hand, the relative lack of alginate particles over the entire tablet's surface when
457 larger particles were used resulted in areas where no polymer was present, as noted by Mitchell *et al.*
458 when working with HPMC matrices (Mitchell et al. 1993). Dissolution medium would enter through
459 these areas and cause a burst release of drug before a protective barrier could be formed. Increasing

460 polymer concentration would allow more particles to cover the tablet surface and reduce the polymer-
461 free areas. With smaller particles, a sufficiently complete gel barrier was formed before significant
462 burst release could occur, even at 10% alginate content.

463 As mentioned previously, drug release from these matrices would be modulated by factors other
464 than particle size. These factors include differences in liquid uptake, swelling, as well as matrix
465 deformation during dissolution. It is also worth pointing that the particle size effect can be masked by
466 the effect of concentration when the alginate content is higher, as has also been observed for HPMC
467 matrices (Velasco et al. 1999; Heng et al. 2001; Mitchell et al. 1993). Finally, similar results of drug
468 release were obtained for NaA presenting different chemical composition demonstrating that the
469 influence of the particle size is not affected by the composition so no relationship was found between
470 these two parameters.

471 At last, the effect of matrix tablet porosity on drug release was also explored by Liew *et al.* Matrix
472 tablets containing 10, 30 and 50% of the same grade of NaA were compressed at different pressures
473 to produce tablets of porosities ranging from 0.08 to 0.2. (Liew et al. 2006) Attempts to produce matrix
474 tablets with porosities below that range resulted in tablet capping upon ejection from the die. Drug
475 release studies showed that there is no significant difference in the release profiles of tablets with the
476 same alginate concentration and different porosities, as drug release appeared to be mainly controlled
477 by the formation of the gel barrier around the matrix tablet. Hence, as seen for HPMC tablets (Velasco
478 et al. 1999; Bettini et al. 1994), drug release is expected to be more closely related to the porosity of
479 the hydrated gel layer, which is independent of the porosity of the dry matrix. Furthermore, changes in
480 compression force only seemed to have a minimal effect on drug release from matrix tablets when the
481 tablets were too soft (about 3 kp) probably due to the lack of powder compaction or consolidation
482 (Rekhi et al. 1999; Bettini et al. 1994).

483 In summary, the work reviewed clearly demonstrates that judicious selection of alginate grade
484 would be essential when designing predictable modified-release dosage forms.

485 **5. The influence of the physicochemical properties of alginic acid on its functionality as an** 486 **excipient for direct compression**

487 Alginic acid is mainly used as disintegrant in tablets designed for immediate drug release. Its
488 disintegrant functionality have been demonstrated to be rapid and comparable to other common
489 commercial superdisintegrants like Glycolys® and Kollidon CL® (Lactose/AA 0.66 seconds; Lactose/
490 Glycolys® 0.53 seconds and Lactose/ Kollidon CL® 0.36 seconds at 200 MPa) (Benabbas et al. 2020;
491 Soulairol et al. 2018; Berry & Ridout 1950). Due to its high sorption capacity and poor solubility in
492 water, its mechanism of disintegration has been assigned to swelling or wicking action
493 (Mohanachandran et al. 2011).

494

495

496 5.1 Factors affecting the tableting properties of alginic acid

497 To our knowledge, only one recent study on the correlation between the tableting properties of AA
498 and its physicochemical properties has been reported (Benabbas et al. 2020). The different tableting
499 properties observed in two batches of AA were associated to the difference on their MW since their
500 composition in uronic acid and particle sizes were similar. While the influence of the MW on the
501 mechanical properties of other natural polymers such as cellulose microcrystalline and chitosan are
502 known (Thoorensa et al. 2015; Picker-Freyer & Brink 2006); this study described for the first time that
503 the determination of the MW of AA seems key for applications in direct compression, and in particular
504 for obtaining tablets with reproducible strength. The average molecular weights were estimated by
505 viscosimetry and SEC by dissolving the AA samples in 0.1M NaCl solution after complete
506 neutralization of the carboxylate groups by addition of NaOH (1 M). Results showed a MW of 19 800
507 g/mol and 10 400 g/mol for AA2 and AA1, respectively. This implies an average chain length of about
508 113 residues for AA2 and 59 for AA1. Alginic acid presenting the lowest MW exhibited the highest
509 tablet strength and presented the lowest elastic recovery after decompression. That was related to the
510 higher presence of GG residues in AA2 compared to AA1 which may lead to greater intramolecular
511 hydrogen bonding formation, thereby limiting chains mobility during compression which could explain
512 the lower compactability and higher elastic recovery of AA2 tablets. This is in agreement with the
513 results obtained by Schmid in which NaA presenting higher degree of polymerization gave tablets
514 which deformed more elastically than the NaA with lower degree of polymerization (Schmid & Picker-
515 Freyer 2009). Along the same lines, chitosan possessing the lowest MW presented higher and easier
516 deformation during compression and formed tablets which exhibited higher crushing forces (Picker-
517 Freyer & Brink 2006; Alakayleh et al. 2016). However, this trend was not followed by cellulose
518 microcrystalline and gelatin which provided harder tablets when the MW was increased (Kokil et al.
519 2004; Shlieout et al. 2002). Thus, it seems that the chemical nature of the polymer and its molecular
520 composition have a great influence on its particle deformation (elastic, brittle or plastic) and thus on its
521 mechanical behaviour on compression.

522 The swelling force of both materials was also demonstrated different with AA2 being 3 times
523 higher than that of AA1 (Benabbas et al. 2020). This difference was also attributed to the Mw
524 distinctness, as AA2 possesses more uronic acid repeating units; it presents a tendency to hydrate
525 better and to absorb more water than AA1 whose molecular chain is shorter. It is interesting to
526 highlight that no difference was observed between the two batches regarding disintegration time
527 despite the difference found in their swelling force. This was explained by the AA promoting
528 disintegration mainly by capillary action and weakly by swelling (Soulaïrol et al. 2018).

529 Process parameters, such as the drying conditions used to prepare acid alginic xerogels from
530 NaA, have been demonstrated to have no influence on the tableting ability (Soulaïrol et al. 2018). All
531 xerogels obtained by oven or rotary evaporation drying methods resulted in tablets with mediocre
532 tensile strength (lower than 2 N mm⁻² at 400 MPa compaction pressure), indicating that the
533 cohesiveness of the xerogels was not influenced by the drying method. The poor tableting ability of AA

534 was explained by its elastic properties towards compression as; in general, elastic materials present a
535 poor cohesion in compression.

536 To date, the effect of other parameters such as concentration in the tablet formulation,
537 composition or particle size on the tableting properties of AA has not been explored. Thus, further
538 work certainly needs to be done in order to build a comprehensive knowledge of the properties-
539 functionality relationship that will allow the design of high quality tablets with consistent performance.
540 On the other hand, in order to expand the use of AA as a direct compression excipient, researchers
541 have explored different strategies to improve the poor mechanical properties and flowability of AA.

542 **5.2 Strategies to improve the properties of alginic acid as direct compression excipient**

543 Despite the proven interest of AA as excipient promoting disintegration, the use of this material
544 remains limited due to certain fall-backs such as poor powder flowability and low tablet hardness,
545 indeed the compactability of alginates has been demonstrated lower than other polysaccharides also
546 used as pharmaceutical excipients such as chitosan and carrageenan (Picker-Freyer & Brink 2006;
547 Picker-Freyer 2005). Thus, a solution proposed to enhance the flowability and poor mechanical
548 properties of AA was the development of a co-processed excipient prepared from AA and cellulose
549 microcrystalline (MCC101) using a laboratory scale high-shear granulator. The concept co-processing
550 has been described as any combination of two or more excipients by physical methods which not lead
551 to the formation of covalent bonds (Rojas et al. 2012). Effects of the two components ratio, the amount
552 of added water or binder during granulation and the particle size, on the properties of the prepared co-
553 processed excipient were investigated. The optimal granule and tablet properties were obtained using
554 a ratio of 10% of AA, 90% of MCC101 and 70% of water. The co-processed product possessed good
555 tableability, enhanced powder flowability and a considerable faster disintegration time in comparison
556 to the primary materials and other commercial co-processed materials such as Prosolv® ODT (6.50
557 sec for AA-MCC vs 16.83 sec for Prosolv at 100 MPa and 11.66 sec for AA-MCC vs 147.7 sec for
558 Prosolv at 200 MPa) (Benabbas et al. 2021).

559 Another way to improve the drawbacks of AA as pharmaceutical excipient was its esterification, a
560 chemical modification commonly used to enhance the functionality of other excipients such as
561 starches, pectins or cellulose (Ačkar et al. 2015; Salbu et al. 2010; Edgar 2007). An increase in the
562 degree of methylation yielded tablets with higher tensile strength and better compressibility (Sanchez-
563 Ballester et al. 2020). Moreover, modified alginates exhibited extended disintegration times compared
564 to native AA due to the introduced hydrophobicity (< 15 min for alginates presenting a degree of
565 methylation 16-57 %) and times up to 45 min for alginates presenting a degree of methylation of 76%.
566 It was also found that esterification induced greater plastic deformation and that this change in the
567 deformation behaviour of the modified materials can be important for enhancing their tableability. This
568 was corroborated by the direct relationship found between tensile strength and degree of methylation;
569 thus, tensile strength of the mini-tablets increased with the degree of methylation. A similar trend was
570 observed in the plastic deformation compactability relationship of methoxylated pectins, with higher
571 degree of methoxylation resulting in stronger pectin's compacts (Kim et al. 1998).

5.3 Factors affecting the biopharmaceutical and gelling properties of alginic acid tablets

In order to get a better understanding of the disintegration mechanism of AA, the water uptake kinetics and swelling of AA xerogels obtained using different drying conditions have been studied (Soulairol et al. 2018). Results showed that the drying method had an influence in the water absorption capacity of AA with higher water absorption observed for samples dried in the oven (6.6 ± 0.1 expressed in grams of water absorbed per grams of polymer (Wg/Pg)) compared to 5.0 ± 0.1 Wg/Pg for samples dried in the rotary evaporator. This was explained by a combination of two factors; firstly, an increased internal porosity was obtained for xerogels dried in the oven which facilitates the penetration of water by capillary action, allowing the absorption of larger volumes of water. And secondly, by the presence of free carboxylic acids in the AA which also favours polymer hydration and therefore increases its water uptake kinetics (Moreton 2009). This capability of materials to interact strongly with water is essential for disintegration functionality. Moreover, at pH 5.5, pure AA systems showed more significant swelling than binary systems containing calcium alginate (CaA and AA/CaA) due to the larger force created by the electrostatic repulsions between the ionized carboxyl groups (pKa 3.5-3.7). All these observations had an impact on disintegrating times, and the shortest times were registered for AA (15-20 sec) and the longest for the CaA system (*c.a.* 1 min). Thus, the disintegration time seems to be related to the water uptake kinetics' rather than to the swelling force suggesting that the factor leading the disintegration mechanism of AA is water wicking into the matrix of the tablets. Moreover, while the disintegration performance of CaA has been demonstrated to be highly dependent of the medium composition, this effect was not observed in the case of AA (Berardi et al. 2021).

Other work realized on swellable drug polyelectrolyte matrices (SDPM) of acid alginic alone or combined with NaA for the delivery of atenol, metoclopramide and propranolol demonstrated that water wicking into the matrix tablets was not the only phenomena driving the disintegration as erosion of the hydrogel layer was also playing a key role in the main delivery process (Ramírez Rigo et al. 2006).

The effect of the chemical composition, sequence and MW of different alginate samples on the final properties of AA gels have been also reported (Draget et al 1994; 1996). Alginates with comparable lengths of uronic acid blocks showed that a high content of guluronic acid blocks resulted in gels with significantly higher strength and six times larger apparent Young's moduli than gels made from mannurate-rich samples. These results were explained by a combination of factors such as the spatial arrangements of the monomers along the polymer chain, which contributes to the formation of stability-enhancing intermolecular bonds; and to the greater entropy loss observed when more flexible mannuronic acid blocks are aligned into junctions compared to more rigid guluronic blocks that make the arrangement process less favourable. A high fraction of alternating sequences formed gels of low strength explained by its inability to create stable intermolecular bonds.

Thus, since homopolymeric regions seem to be essential for AA gel formation, it is reasonable to postulate that cooperative processes are involved in the stabilization of intermolecular junctions (Stokke et al. 1991; Andriamanantoanina & Rinaudo 2010). Finally, Draget *et al.* also established a

611 relationship between AA gel strength and its MW with gel strength increasing with an increase in the
612 MW (Draget et al. 2000).

613 Other parameters such as particle size, which have been found to affect the effectiveness of
614 slightly swelling disintegrants such as potato and rice starch when mixed with magnesium stearate
615 before compression, have not yet been studied for AA. To note that this effect was much less
616 pronounced for tablets containing highly swelling disintegrants such as sodium starch glycolate
617 (Smallenbroek et al. 1981).

618 **6. Conclusion**

619 This review brings together for the first time the work performed on the applicability of alginic acid
620 and sodium alginate as excipients for direct compression in order to get a better insight into the
621 relationship between their structure and their mechanical and biopharmaceutical performances. Due to
622 their safety, abundance and biodegradability, alginic acid and its salts are already broadly used as
623 ingredients in the cosmetic, pharmaceutical and food industries. Despite their wide interest, natural
624 materials such as alginates are exposed to a high variability determined by different parameters such
625 as the source or the extraction method. As the structure of alginates affects both gelling and
626 mechanical properties, the current interest in a good physicochemical characterization goes beyond
627 fundamental reasons, towards the necessary complete understanding of the relationship between
628 alginates' structure and their functionality. Although several studies have illustrated how differences in
629 parameters such as the chemical composition, molecular weight distribution or particle size of sodium
630 alginate can clearly affect its functionality, only a few of them focus on the compression process, the
631 storage and the behaviour of alginates in powder form. Moreover, pharmacopoeia standards do not
632 currently include specifications and tests to analyze these variations. For alginic acid, studies
633 performed on the effect of these parameters on its properties are even scarcer; thus, additional
634 information will indeed be needed to best exploit its range of capabilities as a pharmaceutical excipient
635 for direct compression. Finally, the introduction of novel drug moieties to the pharmaceutical market
636 leads to the need for new excipients with varied characteristics. Thus, investigating further the
637 properties of already marketed excipients such as alginates can be an easy and cost-effective strategy
638 to achieve this. To reach this goal, it will be essential to implement quality-by-design (QbD) product
639 development strategies, with increased emphasis on detailed characterization of biosourced
640 excipients, to achieve robust formulations and processes that enable the design of high-quality drug
641 products with consistent performance.

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