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Review

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

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

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

1. Introduction

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

Direct compression is generally the preferred mode for tablet manufacturing; in this process, the dry constituents, active ingredients and excipients, are thoroughly mixed and then compressed into tablets. The assets of direct compression are well-known, the most relevant being the reduction in the 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.

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

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

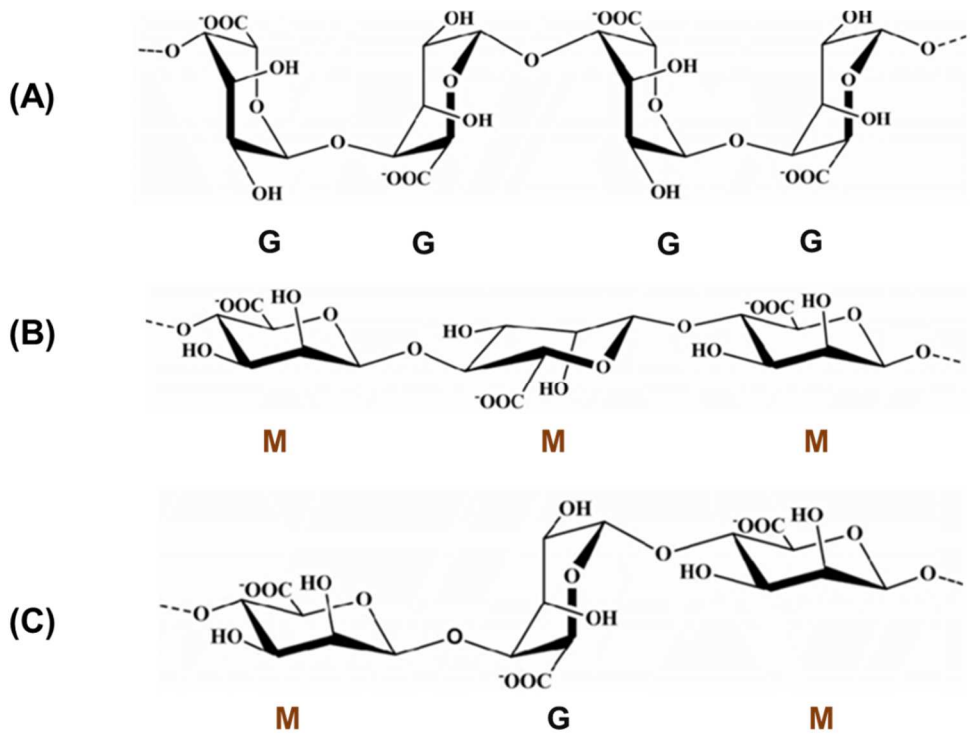

Figure 1 (a) Homopolymeric blocks of poly-α-1,4-L-guluronic acid (GG); (b) Homopolymeric blocks of poly-β-1,4-D-mannuronic acid (MM); (c) Heteropolymeric blocks of alternating M and G residues.

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

Alginates obtained from different algae species, season and place of harvesting will differ significantly in their chemical composition (mannuronic/guluronic (M/G) ratio), structural/block organization, and physicochemical properties (molecular weight, rheological characteristics, moisture content, particle size distribution, purity, etc.). The extraction method and process parameters (temperature, time of extraction, alkali concentration and pre-treatment) have also shown an impact on the properties of the produced alginate (Vauchel et al. 2008; Chee et al. 2011). For instance, alginates' rheological properties have been found to be greatly dependent on the processing temperature (Vauchel et al. 2008). Thus, although an increase of the treatment temperature can improve the extraction yield, a decrease of viscosity was also observed (Hernandez-Carmona et al. 2013). The molecular weight (MW) can also differ depending on the extraction method used (Borazjani et al. 2017). In a study reported by Gomez *et al.*, three routes of precipitation of sodium alginate from *Macrocystis pyrifera* using ethanol, HCl or $CaCl_2$ were compared. Analysis of the different products showed that while the ethanol route had the lowest number of steps and displayed the best performance; the $CaCl_2$ route gave alginates with the lowest MW and poorer mechanical properties (Gomez et al. 2009). Moreover, since alginates are obtained from a natural source, a variety of impurities such as heavy metals, proteins and endotoxins may potentially be present. For applications in the food and beverage industry, low levels of these impurities are not a problem, but for pharmaceutical applications and in particular, when the alginate is used in parenteral administration, these impurities must be removed (Gombotz & Wee 1998). In view of this, limits not to be exceeded are recommended in the European Pharmacopeia for sodium alginate (NaA) and alginic acid (AA) (European Pharmacopeia 2017).

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

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

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

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

2. Structure of alginates

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

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

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

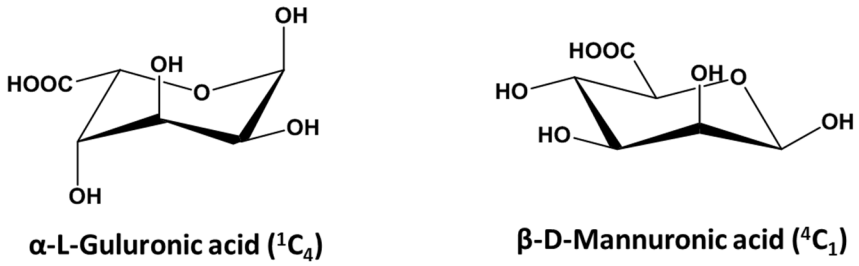

Figure 2. Conformational structure of alginate monomers.

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

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

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

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

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

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

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

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

3.1 Determination of the composition and primary structure

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

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

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

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

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

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

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

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

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

3.2 Determination of Molecular Weight and Molecular weight distribution

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

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

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

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

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

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

4.1 Sodium alginate as direct compression excipient

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

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

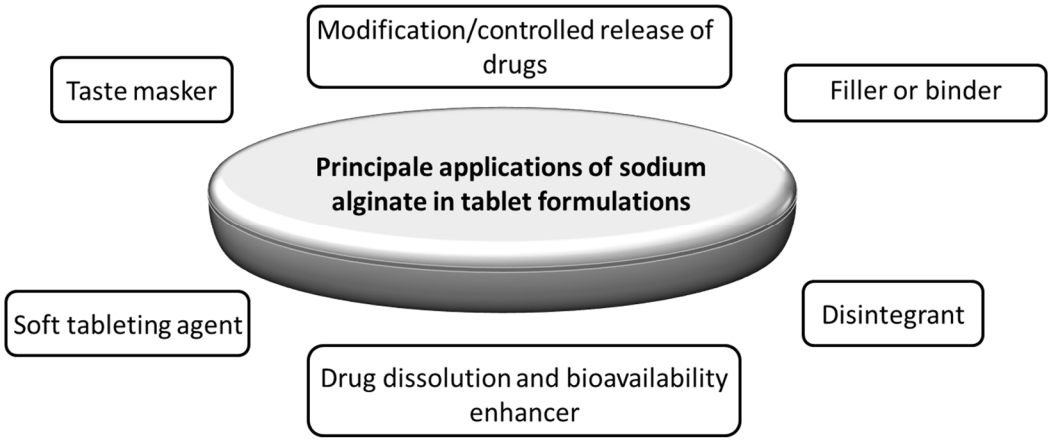

Figure 3. Overview of the main roles of sodium alginate in the formulation of solid oral tablets.

4.2 Sodium alginate structure - tablet compression properties relationship

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

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

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

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

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

4.3 Factors affecting the biopharmaceutical properties of sodium alginate tablets

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

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

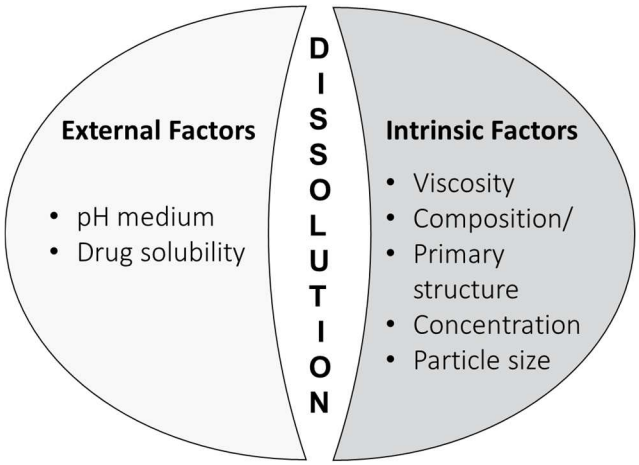

Figure 4. Factors affecting the biopharmaceutical properties of sodium alginate tablets.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5.1 Factors affecting the tableting properties of alginic acid

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

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

Process parameters, such as the drying conditions used to prepare acid alginic xerogels from NaA, have been demonstrated to have no influence on the tabletability (Soulairol et al. 2018). All xerogels obtained by oven or rotary evaporation drying methods resulted in tablets with mediocre tensile strength (lower than 2 N mm^{-2} at 400 MPa compaction pressure), indicating that the cohesiveness of the xerogels was not influenced by the drying method. The poor tabletability 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 tabletability, 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 tabletability. 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).

572 **5.3 Factors affecting the biopharmaceutical and gelling properties of alginic acid tablets**

573 In order to get a better understanding of the disintegration mechanism of AA, the water uptake
574 kinetics and swelling of AA xerogels obtained using different drying conditions have been studied
575 (Soulairol et al. 2018). Results showed that the drying method had an influence in the water
576 absorption capacity of AA with higher water absorption observed for samples dried in the oven (6.6 ±
577 0.1 expressed in grams of water absorbed par grams of polymer (Wg/Pg)) compared to 5.0 ± 0.1
578 Wg/Pg for samples dried in the rotary evaporator. This was explained by a combination of two factors;
579 firstly, an increased internal porosity was obtained for xerogels dried in the oven which facilitates the
580 penetration of water by capillary action, allowing the absorption of larger volumes of water. And
581 secondly, by the presence of free carboxylic acids in the AA which also favours polymer hydration and
582 therefore increases its water uptake kinetics (Moreton 2009). This capability of materials to interact
583 strongly with water is essential for disintegration functionality. Moreover, at pH 5.5, pure AA systems
584 showed more significant swelling than binary systems containing calcium alginate (CaA and AA/CaA)
585 due to the larger force created by the electrostatic repulsions between the ionized carboxyl groups
586 (pKa 3.5-3.7). All these observations had an impact on disintegrating times, and the shortest times
587 were registered for AA (15-20 sec) and the longest for the CaA system (*c.a.* 1 min). Thus, the
588 disintegration time seems to be related to the water uptake kinetics' rather than to the swelling force
589 suggesting that the factor leading the disintegration mechanism of AA is water wicking into the matrix
590 of the tablets. Moreover, while the disintegration performance of CaA has been demonstrated to be
591 highly dependent of the medium composition, this effect was not observed in the case of AA (Berardi
592 et al. 2021).

593 Other work realized on swellable drug polyelectrolyte matrices (SDPM) of acid alginic alone or
594 combined with NaA for the delivery of atenol, metoclopramide and propranolol demonstrated that
595 water wicking into the matrix tablets was not the only phenomena driving the disintegration as erosion
596 of the hydrogel layer was also playing a key role in the main delivery process (Ramírez Rigo et al.
597 2006).

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

608 Thus, since homopolymeric regions seem to be essential for AA gel formation, it is reasonable to
609 postulate that cooperative processes are involved in the stabilization of intermolecular junctions
610 (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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