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Inter-Grade and Inter-Batch Variability of Pharmaceutical-Grade Sodium Alginate

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INTER-GRADE AND INTER-BATCH VARIABILITY OF PHARMACEUTICAL-GRADE SODIUM ALGINATE

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ABSTRACT

INTER-GRADE AND INTER-BATCH VARIABILITY OF

PHARMACEUTICAL-GRADE SODIUM ALGINATE

By

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December 2011

Dissertation Supervised by Lawrence H. Block, Ph.D. and Peter Wildfong, Ph.D.

Polymeric excipients are generally the least well-characterized components of pharmaceutical formulations. The aim of this dissertation work is to facilitate the quality-by-design (QbD) approach to pharmaceutical formulation and manufacturing by evaluating the inter-grade and inter-batch variability of pharmaceutical-grade polymeric excipients. Sodium alginate, a widely used polymeric excipient, was selected for evaluation using appropriate analytical methods and test conditions, especially rheological methods. The materials used were six different grades of sodium alginate and an additional ten batches of one of the grades.

To compare the six grades, steady shear measurements were conducted on solutions at 1, 2, and 3% w/w, consistent with their use as thickening or binding agents.

Small amplitude oscillation (SAO) measurements were conducted on sodium alginate solutions at higher concentrations (4-13% w/w) corresponding to their use in controlled release matrices. In order to compare the ten batches of one grade, steady shear and SAO measurements were performed on their solutions at 2% w/w and 8% w/w, respectively. Results show that rheological properties of sodium alginate solutions are influenced by both molecular weight and chemical composition of sodium alginate. "One-point" apparent viscosity data obtained at one low concentration and one shear rate is not representative of the complex rheological behavior of various grades of sodium alginate solutions at higher concentrations or other shear rates. The potential interchangeability of these different grades used as thickening or binding agents could be established by comparing the apparent viscosities of their solutions as a function of both alginate concentration and shear conditions. For sodium alginate used in controlled release formulations, both steady shear (at one low concentration, *e.g.*, 2% w/w) and SAO measurements (at one high concentration indicative of polymer gel state, *e.g.*, 8% w/w) are recommended to be performed on sodium alginate solutions to ensure interchangeability. Furthermore, among batches of the same grade, significant differences in rheological properties were observed, especially at the high solution concentration (*i.e.*, 8% w/w). In summary, inter-grade and inter-batch variability of sodium alginate can be determined using steady shear and SAO methods.

The influence of inter-grade and inter-batch variability of sodium alginate on the functionality of sodium alginate used in matrix tablets was investigated with a focus on compression properties, swelling, erosion behavior of alginate matrix tablets, and drug release from matrix tablets. The compression behavior of four grades and three batches of

sodium alginate were studied by compaction energetics, out-of-die Gurnham, and out-of-die Heckel analysis. It was found that sodium alginates deform less plastically than microcrystalline cellulose (MCC PH102) but similar to lactose anhydrous. Sodium alginates also demonstrate more elastic deformations during compression than both MCC PH102 and lactose anhydrous. Compacts prepared from multiple batches of the same grade varied in porosity. The same tensile strength of compacts can be achieved by compressing the multiple batches to the same porosity.

Sodium alginate tablets undergo both swelling and erosion in water. Grades with substantially higher apparent viscosities at low solution concentration exhibit a higher percentage of water uptake and a low percentage of erosion. Those batches not significantly different in their apparent viscosities at low solution concentration but significantly different in viscoelasticity at high solution concentrations do demonstrate significant differences in their swelling and erosion behavior. Acetaminophen release from sodium alginate matrix tablets prepared from the four grades and three batches can be well described by a zero-order equation. Significant differences in release profile were observed among various grades and batches.

In conclusion, the inter-grade and inter-batch variability of sodium alginate has a significant influence on the swelling, erosion, and drug release behavior of sodium alginate matrix tablets. Apparent viscosities of sodium alginate solution at low concentration alone are not sufficient to predict the functionality of sodium alginate used in matrix tablets. Viscoelastic properties of sodium alginate solutions at high concentrations indicative of polymer gel state are appropriate to be characterized.

Further study was conducted to determine whether sodium alginate solutions' rheological parameters are relevant to sodium alginate's use in the formulation of calcium alginate gels. Among the grades with similar guluronic acid percentage (%G), there is a significant correlation between gel fracture force and apparent viscosity. However, the results for the partial correlation analysis for all six grades of sodium alginate show that gel fracture force is significantly correlated with %G, but not with the rheological properties of the sodium alginate solutions. Studies of the ten batches of one grade of sodium alginate show that apparent viscosities of their solutions do not correlate with gel fracture force while tan δ values are significantly, but minimally, correlated to gel fracture force. Inter-batch differences in the rheological behavior for one specific grade of sodium alginate are insufficient to predict the corresponding calcium alginate gel's mechanical properties.

In summary, rheological methods, including steady shear and small amplitude oscillation, are able to identify the inter-grade and inter-batch variability of sodium alginate. Inter-grade and inter-batch variability of sodium alginate could lead to substantial differences in the functionality of sodium alginate in matrix tablets and in calcium alginate gels. Rheological properties of sodium alginate in solution are suggestive of its functionality as thickeners, or as controlled release agent. However, rheological properties of sodium alginate in solution do not seem to be sufficient to predict the mechanical properties of the corresponding calcium alginate gels.

DEDICATION

To my parents, Fu Nanyou and Xu Jinying, my wife, Hao Fu, and our daughter Isabelle

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CHAPTER 1. INTRODUCTION

STATEMENT OF PROBLEM

In recent years, the FDA has made substantial efforts in implementing the concept of "Quality by Design" (QbD). QbD emphasizes that quality cannot be tested into a pharmaceutical product, but rather that quality should be built into a product by virtue of a thorough understanding of the product ingredients and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks.[1] A key component of the QbD concept is "Design space" — defined in the ICH Q8 (R1) guidance document as the "multidimensional combination and interaction of input variables (*e.g.,* material attributes) and process parameters that have been demonstrated to provide assurance of quality." As a result, Quality-by-Design (QbD) principles necessitate the establishment of a design space for each pharmaceutical product encompassing, in part, the active pharmaceutical ingredient(s) (APIs), the excipients, and the unit operations employed to produce the finished product.[2]

Most of the attention in the pharmaceutical industry on product quality has focused on the physicochemical properties of APIs and the process variables of the various unit operations involved in a product's manufacture rather than on excipients. It is realized that variability in the APIs could be minimized by controlling physical or physicochemical parameters such as particle size distribution, polymorphic form, etc. Also, the variability in various unit operations could be minimized with a better understanding of the engineering principles that are responsible for variations in the outcome. In contrast, minimal attention has been paid to excipients and their variability.[3]

Excipients are defined by the USP as any component, other than active substances, intentionally added to the formulation of a dosage form. Excipients are included in a drug dosage form or delivery system to aid in manufacturing, to protect the APIs from degradation, to enhance stability, bioavailability, or patient acceptability, to assist in product identification, or to enhance any other attributes of the overall safety and effectiveness of a pharmaceutical product during storage and use. Furthermore, excipients in drug dosage forms and delivery systems can markedly affect the biopharmaceutical and pharmacokinetic properties of the associated APIs.[4,5] In one case, for example, a change of calcium sulfate dihydrate to lactose in phenytoin capsules resulted in patient intoxication due to high phenytoin blood concentration.[3] Nonetheless, excipients tend to be the least well-characterized components of the design space. At present, excipients are not always viewed for what they are, *i.e.*, relatively impure, complex materials that, in the case of polymeric excipients, are not monodisperse. Since excipients are often poorly characterized physically and chemically, their impact on product variability is under-appreciated.

Pharmaceutical excipients tend to exhibit inter- and intra- manufacturer variability, owing largely to raw material variability.[6] To monitor and control the possible variability of excipients, manufacturers typically rely on compendial specifications listed in individual monographs for pharmaceutical excipients in the United States Pharmacopoeia – National Formulary (USP–NF).[7] However, pharmacopoeial specifications are primarily designed for assuring the identity and purity of pharmaceutical excipients, and not their functionality. There are a number of published studies attesting to the inequivalence of pharmaceutical excipients from multiple sources

or to the variability of multiple batches of an excipient from the same manufacturer, despite their adherence to USP–NF specifications.[8-24] For example, it was reported in 2010 that sodium lauryl sulfate (SLS) from two different sources: Spectrum Chemical, (Gardena, CA, USA) and Cognis Corporation (Cincinnati, OH, USA), both of which were labeled NF grade, differed significantly with respect to their effects on enhancing the solubility of a model drug and the drug dissolution rate from tablets.[24] The NF addresses this issue by stating: "Because of differing characteristics not standardized by this formulary, all sources and types of some excipients may not have identical properties with respect to use in a specific formulation. To assure interchangeability in such circumstances, users may wish to ascertain final performance equivalency or determine such characteristics before use."[25]

Polymeric excipients, especially polymers extracted from natural resources, tend to exhibit inter-grade and intra-grade variability in their molecular weight distribution and chemical composition.[26] The variability in the physicochemical properties of polymeric excipients could result in substantial differences in the final product performance.[8-16,21,27,28] To further explore the issues of polymeric excipient variability, this dissertation focuses on a widely used, but poorly characterized polymeric excipient, sodium alginate. Sodium alginates are linear, unbranched, amorphous polysaccharides extracted from various types of seaweed. They are copolymers of β-D-mannuronic acid (*M*) and α-L-guluronic acid (*G*) linked to each other by 1→4 glycosidic bonds. The *M* and *G* units in the alginates may be randomly or non-randomly arrayed as heterogeneous or homogeneous sequences.

Sodium alginates have wide applications in the pharmaceutical and biomedical areas due to their abundance, low price, and compatibility with biological systems.[29] Pharmaceutically, sodium alginates are generally used as binding agents in tablets, as suspending and thickening agents in water-miscible gels, lotions and creams, as emulsion stabilizers, or as gel-forming agents in combination with divalent metal ions such as calcium.[30] Of particular interest is their potential in the development of alginate-based controlled release drug delivery systems, such as matrix tablets, microcapsules, *etc*.[29]

According to a 2002 review by Tonnesen and Karlsen,[29] more than 200 different alginate grades varying in molecular weight and chemical composition are commercially available from manufacturers. The heterogeneity of commercial pharmaceutical-grade alginates reflects differences among the botanical sources, seaweed harvesting locations, the season of harvesting, the plant parts employed, and the processing methods used. Current pharmacopoeial standards for sodium alginate include the following specifications and tests: identification (qualitative determination of the existence of sodium alginate by forming gel with calcium cations or with addition of sulfuric acid), microbial limits, loss on drying, total ash, arsenic, lead, heavy metals, and assay (quantitative determination of the amount of sodium alginate by a titrimetric method). However, these specifications and tests do not enable the characterization of variations in the molecular weight distribution and/or chemical composition of sodium alginate. As these variations can markedly affect the processability or performance of a sodium alginate-containing pharmaceutical product,[31,32] it is important to find effective methods to better characterize sodium alginate.[1]

An effective method of excipient characterization should reflect the excipient's behavior during processing and its functionality in potential formulations. Since sodium alginates are mostly used as thickeners and gel-forming agents in both conventional and controlled release formulations, their processability and functionality can be related to their rheological behavior in solution. Rheological methods have many advantages over other methodologies for the characterization of polymer solutions: relatively simple sample preparation, short times required for tests, and direct measurement of polymer behavior under conditions expected to be encountered during formulation processing or product storage or use. Despite their utility in characterizing functionality, rheological testing of sodium alginate solutions is not specified in the United States Pharmacopoeia. Furthermore, even when excipient manufacturers do supply rheological data for sodium alginates, they typically only report the *apparent* viscosities of solutions at *one* specific concentration at *one* shear rate, and at *one* temperature — "one-point" measurements — as if the alginates' solutions' rheological characteristics were those of Newtonian fluids. In fact, the typical rheological behavior of many polymer solutions is highly concentration-dependent, encompassing properties of those ranging from Newtonian fluids (at dilute concentrations), to those of shear-thinning non-Newtonian fluids (at intermediate concentrations), to those exhibiting viscoelastic behavior (at high concentrations).[33,34] Additionally, the shear rates encountered in pharmaceutical manufacturing and in product use can vary considerably, ranging from 10^{-3} to 10^{4} s^{-1}.[35] Thus, "one-point" apparent viscosity measurements provide little or no insight into the selection of suitable polymer grades for a specific formulation or manufacturing process.[36] A comprehensive rheological evaluation of sodium alginate solutions is

warranted in order to facilitate the identification of criteria that would allow grade-to-grade or batch-to-batch comparison.

Although a number of studies have been published on the rheological behavior of sodium alginate solutions,[37-47] most of the sodium alginates employed in these studies were not pharmaceutical grades. For that matter, explicit recommendations have not been made in the literature as to the rheological methods that would be most appropriate for polymeric excipient evaluation relative to pharmaceutical processing or formulation performance. In addition, the previous studies were limited to the rheological characterization of sodium alginate solutions with concentrations lower than 5% w/v. Sodium alginate solutions at these low concentrations exhibit fluid-like behavior, whereas sodium alginate solutions at higher concentrations display a more substantial viscoelastic character. Process and product quality control during formulation development necessitate characterization of the rheological behavior of the excipient utilizing experimental conditions and excipient concentrations appropriate to the formulation under consideration.

Hypothesis and Objectives

The central hypothesis of this dissertation is that a comprehensive analysis of the rheological behavior, including apparent viscosity and viscoelasticity of sodium alginate solutions, will allow the identification of the inter-grade or inter-batch variability of pharmaceutical-grade sodium alginate.

The objectives of this dissertation are to:

1. Determine the inter-grade and inter-batch variability of sodium alginate using rheological methods including steady shear and small amplitude oscillation.
2. Investigate how inter-grade and inter-batch variability of sodium alginate grades and batches affect the compression behavior of sodium alginate and the functionality of sodium alginate matrix tablets, allowing correlation between rheological properties of sodium alginate in solution to its functionality in matrix tablets.
3. Examine the correlation between rheological properties of sodium alginate in solution and calcium alginate gel properties.

LITERATURE REVIEW

EXCIPIENT VARIABILITY

According to the USP-NF (General Chapters <1078>) definition, excipients are "any substances, other than the active drug or product, that have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use." Excipients are not inert but play an essential role in the development and manufacture of pharmaceutical products. Excipients enable the active pharmaceutical ingredients (APIs) to be formulated and/or manufactured as an efficacious drug product that can be administered safely to the patient. Generally, the proportion of excipients in the drug formulation is substantially larger than that of the API. As a result, excipient properties often dictate the formulation behavior, making it critical to understand their functionality in a given formulation, and to develop effective methods for the characterization and control of the excipients with respect to their functionality for consistent product performance.

Excipient functionality spans a broad range of applications including tablet diluents, lubricants, disintegrants, binders, surfactants, plasticizers, coloring agents, thickening agents, controlled release agents, preservatives, *etc*. The selection of the most appropriate excipients is crucial, since excipients can influence the compatibility, stability, optimum shelf-life, and the *in vivo* performance of the pharmaceutical products. Pharmaceutical excipients are required to conform to the compendial specifications as

listed in the monographs in USP-NF. However, as Shangraw noted in 1987, compendial standards have traditionally focused on identity, quality, purity, packaging, and labeling, allowing standards for drugs to take precedence over standards for excipients.[48] This disparity is still evident today, in spite of FDA's revision and support of the *ICH Guidance for Industry — Q8(R2) Pharmaceutical Development*, which suggests that "those aspects of drug products, *excipients*.....that are critical to product quality should be determined and control strategies justified."[49]

Quality-by-design (QbD) principles necessitate the establishment of a design space for each pharmaceutical product encompassing the active pharmaceutical ingredient(s) (APIs), the unit operations, and the excipients.[2] Unlike APIs, excipients tend to be less well characterized, and yet constitute the major components in many drug formulations. In fact, polymeric excipients could be a major source of variability in pharmaceutical products, as they comprise mixtures of polymers of different molecular weights and chemical composition.[26] To monitor and control the variability of excipients, formulators typically rely on compendial specifications provided for excipients in the USP-NF.[50] However, tests listed in compendial specifications may not be indicative of how an excipient will perform its intended function in a formulation. Furthermore, an excipient may have multiple functionalities in a formulation, *e.g.*, an excipient may function as a tablet binder, thickening agent, controlled release agent in a single product, depending on its use in a formulation, manufacturing process, and/or drug delivery system.[51]

The National Formulary has addressed the variability of excipient functionality in their General Notices and Requirements, stating that: "Because of differing

characteristics not standardized by the National Formulary, all sources or types of some excipients may not have identical properties with respect to use in a specific preparation. To assure interchangeability in such instances, users may wish to ascertain final performance equivalency or determine such characteristics prior to use."[25]

The FDA has also noted that "For an excipient, conformance to compendial specifications alone can be inadequate for performing its intended function in a drug product, and/or for its suitability for use in commercial scale manufacturing (of the drug product), if the critical attributes of the excipient are not similar, when obtained from multiple sources." [52]

Published reports have underscored the inequivalence of pharmaceutical excipients from multiple sources or even multiple batches from the same manufacturer with respect to processability, quality, and performance of the finished drug product, although all of them adhere to USP–NF specifications.[8-24,28] Early in 1987, Reier[8] addressed the issue of reproducibility of excipients from lot-to-lot and vendor-to-vendor. His report investigated the variability of the "same" NF-grade material(s) from multiple suppliers. He found that tribasic calcium phosphate from multiple sources varied in color, flowability, and compressibility, while lactose exhibited inter-manufacturer variability in compressibility and flowability. Magnesium stearate from three separate batches of the same grade was found to be different with respect to particle morphology, particle size, bulk density and specific surface area, and resulted in variable tablet hardness, disintegration time, and drug dissolution. Povidone from various sources has been shown to vary with respect to its effect on tablet dissolution, sorbitol varies with respect to its compressibility, pregelatinized starch shows a varying degree of hydration, and titanium

dioxide varies with respect to solid form and hardness from manufacturer-to-manufacturer.[8]

Doelker *et al*.,[27] investigated the tableting characteristics of NF grade microcrystalline cellulose (MCC) from seven manufacturers. The MCC powders were examined for their moisture content, particle size distribution, true, bulk and tapped densities, and flow properties. The effect of adding a lubricant (0.5% magnesium stearate) on the flow and tableting properties was also evaluated. Large differences in tablet properties (*e.g*., crushing forces of tablets) were generally observed among MCC products from the various manufacturers. In contrast, lot-to-lot variability was much less, and quite acceptable. Whiteman and Yarwood[9] also compared the tableting behavior of microcrystalline cellulose (MCC) from six different manufacturers and observed significant differences in the resultant tablet tensile strength due to possible variations in particle size distribution and surface properties. It was concluded that the compression properties of MCC could not be predicted based on compendial specifications (NF or BP).

Landín *et al*., (1993)[13,28] investigated the physicochemical properties of MCC produced in four different countries, from different types of wood, as raw materials, and three batches of MCC from the same manufacturer that differed in manufacturing process and raw materials. It was evident that MCC produced from different raw materials using different manufacturing processes were significantly different in lignin and hemicellulose content, crystallinity percentage, particle size, and flowability. Subsequent study on the influence of MCC source and batch variation on the tableting behavior and dissolution of

prednisone from MCC tablets showed that the variability in the rate of release of prednisone from the MCC-based tablets was correlated to MCC variability.[14]

Lucisano *et al.*,[10] evaluated two sources of hydroxypropyl methylcellulose (HPMC or hypromellose) used in a sustained-release tablet matrix. The difference in particle size and hydroxypropyl content of HPMC from the two sources led to different polymer hydration rates and hence different dissolution profiles. Dahl *et al.*,[11] conducted a study to elucidate the correlation between HPMC physicochemical properties and the drug release profile from HPMC matrix tablets. Different lots of HPMC 2208 from two suppliers were used in their study. It was found that, irrespective of the supplier, the drug release profile was dependent on the chemical composition of the HPMC 2208, *i.e.*, the higher the hydroxypropyl content, the faster the drug release rate. The authors pointed out that compendial specifications for the hydroxypropyl content of HPMC were too broad for their usage in sustained-release tablet matrix.

Chatlapalli and Rohera[20] used a torque rheometer to study the rheological behavior of wet masses containing hydroxypropyl methylcellulose (HPMC) from two sources (Methocel® [Dow, Midland, Michigan, USA] and Pharmacoat® [Shin-Etsu, Tokyo, Japan]) and diltiazem HCl (DTZ) as the model drug. Distinct differences in the rheological properties of the wet masses were observed, and attributed to the use of the two different HPMCs. The authors suggested that the larger surface area, along with the lower bulk and tapped density of Pharmacoat® might lead to a higher substrate-binder interaction relative to the DTZ-Methocel® system, thus resulting in higher shearing torque during rheological characterization. Based on their findings, the authors suggested that rheological evaluation (which is not specified in USP-NF monograph for HPMC) of

HPMC from multiple sources could provide valuable information on the functionality and interchangeability of these excipients in wet granulation processes, pelletization, and extrusion/ spheronization.

Alvarez-Lorenzo *et al.*[16] compared the physicochemical properties of hydroxypropylcellulose (HPC) from two suppliers, considered nominally interchangeable, at least according to the criteria given in the USP-NF. However, these HPCs showed significant differences in molecular weight, molecular structure, particle size distribution, particle shape, and water affinity. The differences in HPC physicochemical properties resulted in significantly different drug-release profiles of theophylline from HPC-based matrix tablets. The authors suggested that other physical properties that were not specified in the USP-NF, *e.g.*, mean molecular weight and particle size distribution, should be determined for quality control of HPCs used in the manufacture of matrix tablets.

Desai *et al.* [21] reported that HPC from two different sources (Hercules, USA and Nippon Soda, Japan), although both adhering to NF specifications, resulted in hydrochlorothiazide tablet formulations with different drug dissolution profiles. The difference in performance between the two sources of HPC could be explained by their differences in chemical composition. HPC from Hercules had a higher percentage of hydroxypropyl content and a higher degree of molecular substitution than HPC from Nippon Soda. As a result, HPC from Hercules was less hydrophilic and formed a less viscous layer surrounding drug granules, leading to faster drug dissolution rate. Their study emphasized the importance of establishing functional tests for excipients used in

pharmaceutical products. It was suggested in the same paper that a cloud point test could be performed as a routine quality control tool for HPC used in controlled release tablets.

Shah and Augsburger[17,18] noted that the USP-NF monographs for crospovidone do not provide effective specifications which reflect on their functionality. Hence, reliable performance of crospovidone as disintegrant cannot be assumed from different sources meeting USP-NF standards. In their studies, five grades of crospovidone (two grades from ISP, Wayne, NJ, USA and the other three grades from BASF, Florham Park, NJ, USA) were compared and substantial differences in particle size and distribution, surface area, porosity and surface morphology were observed. The differences among the five grades of crospovidone in physical properties resulted in differences in disintegration time and dissolution rate of hydrochlorothiazide from crospovidone-containing dicalcium phosphate tablets. Due to the differences observed in crospovidone from multiple sources meeting NF standards, the authors proposed settling volume, liquid uptake, and disintegration force tests as standard performance tests for crospovidone.

Shah and Augsburger [19] also compared the physical properties of another superdisintegrant, sodium starch glycolate, from three sources. These sodium starch glycolates exhibited differences in particle size, surface area, porosity, surface morphology, and viscosity, although they all adhered to NF specifications. Compendial specifications for sodium starch glycolate do not characterize the physical properties associated with the functionality of sodium starch glycolate as a superdisintegrant.

Zhao and Augsburger[22] investigated the influence of inter-manufacturer variability of croscarmellose sodium on its performance as a superdisintegrant. Croscarmellose sodium from five manufacturers (FMC Biopolymer, USA; DMV

International, Netherlands; Blanver, Brazil; Noviant, Netherlands; and JRS Pharma, USA) was selected for their study. Differences were observed in water uptake, and swelling properties of five sources of croscarmellose sodium in either neutral water or 0.1 N HCl, which were thought to be due to their differences in particle size, total degree of substitution, and the ratio of basic to acidic substituents.

Whiteman and Yarwood[12] evaluated the influence of lactose NF from two different sources on tablet properties in a model formulation and a development formulation. It was found that the difference in mean particle size between these two sources resulted in different tablet tensile strength in both formulations investigated.

Chamarthy *et al.*,[23] compared the functionality of two different lots of soluble starch as compaction aid. One lot was used as received from the vendor and the other lot underwent an extra washing step with acetone. Although these two lots of soluble starch were indistinguishable in particle size, specific surface area, crystallinity, moisture sorption, and IR spectrum, they were very different in their performance as a compaction aid (compressibility and compactibility) under all conditions of compression pressure and storage relative humidity studied. The difference in performance was found to be due to their difference in surface energy. The lot with higher surface energy resulted in compacts with higher tensile strength.

Perez-Marcos *et al.*[15] found that seven lots of Carbomer 934 differed significantly in their rheological characteristics in aqueous dispersions, although these lots did not exhibit appreciable differences in infrared (IR) spectra, density or carboxylic acid group content. The differences in rheological behavior of these seven lots are due to their differences in mean molecular weight. Significant differences between the two most

dissimilar lots were observed in regards to the dissolution profiles of theophylline and hydrochlorothiazide from these Carbomer-based matrix tablets.

More recently, Qiang *et al*.,[24] investigated the effects of sodium lauryl sulfate (SLS) from two different sources: Spectrum (Gardena, CA, USA) vs. Cognis (Cincinnati, OH, USA) on the solubilization of a model drug and its dissolution from tablets. The critical micelle concentration was lower for SLS from Spectrum than that from Cognis due to the difference in impurities. Apparently, the difference in critical micelle concentration between the two sources of SLS resulted in substantially different degrees of solubilization of the model drug.

In summary, these previous studies have all emphasized the importance of evaluating and controlling the critical excipient properties, to ensure that consistent product performance is achieved. According to personal communications with experienced scientists in the excipient industry, it is possible to control excipient variability within a narrower range. However, greater control of excipient variability is associated with a much higher cost, which is usually unacceptable to both excipient manufacturers and the pharmaceutical industry. Nonetheless, steps need to be taken to ensure that the variability of excipients does not adversely affect manufacturing processes and product efficacy. The practicality and ultimate acceptability of ICH Q8 and the QbD concept will depend on the realization that the excipient variability (inequivalence) issues raised over the years are not of little consequence; they are not going to go away. Additional studies of excipient variability and functional performance must be undertaken. Not every drug dosage form or drug delivery system will be affected in the

same way by excipient variability, but we need to know the extent of the problem early on in the development process.[53]

SODIUM ALGINATE

Production

Commercial sodium alginates are produced from various seaweed genera including *Ascophyllum*, *Durvillaea*, *Eklonia*, *Laminaria*, *Lessonia*, *Macrocystis*, *Sargassum*, and *Turbinaria*. Among these eight genera, *Ascophyllum*, *Laminaria*, and *Macrocystis* are the most widely harvested.[54]

Alginic acid was first discovered by E. C. C. Stanford, a British pharmacist, in 1883. Commercial production of alginates did not begin until Kelco was founded in 1929 in California. Since then the alginate industry has grown with major producers being the United States, the United Kingdom, Norway, Canada, France, Japan, and China. In the United States, FMC Biopolymer is the major producer of alginates after buying the alginate section from ISP in 2008. The production of alginates in 2009 was 26,500 tons with a value of about US$318 million.[55]

In seaweed, alginic acid is present predominantly as its calcium salt, although sodium, magnesium, and potassium salts also exist. The chemistry of the extraction processes of sodium alginate from seaweed is relatively simple, *i.e.*, to turn insoluble calcium salts into soluble sodium alginate (Alg = alginate):

$$Ca(Alg)_2 + 2Na^+ \rightarrow 2NaAlg + Ca^{2+}$$

However, the difficulties of the extraction processes arise from the physical separations required to filter slimy residues from viscous solutions or to separate

gelatinous precipitates from the large amounts of water within their gel structure which are resistant to both filtration and centrifugation.

There are two alternative extraction processes employed in the manufacture of sodium alginate from seaweed. In the first process, the principal intermediates are calcium alginate and alginic acid. The intermediate calcium alginate can be precipitated in a fibrous form, which can be readily separated. After separation, calcium alginate can then be converted into alginic acid, which is fibrous and can be readily separated. Furthermore, some calcium alginate can be allowed to remain in the sodium alginate product to control the viscosity of the final product. In the other process, no calcium alginate is formed; only alginic acid is produced. The disadvantage of the latter process is that alginic acid forms a gelatinous precipitate which is very difficult to separate, and the overall losses of alginic acid are generally greater than in the former process. In addition, the removal of water from within the gel structure of the separated alginic acid also presents difficulties in this process. Alcohol is usually used as a solvent for the conversion of alginic acid to sodium alginate. The use of alcohol makes the process more expensive and may lead to additional testing for organic solvent residues in the final product.

The details of the calcium alginate extraction process are listed in Figure 1 and described in the following paragraphs.[54]

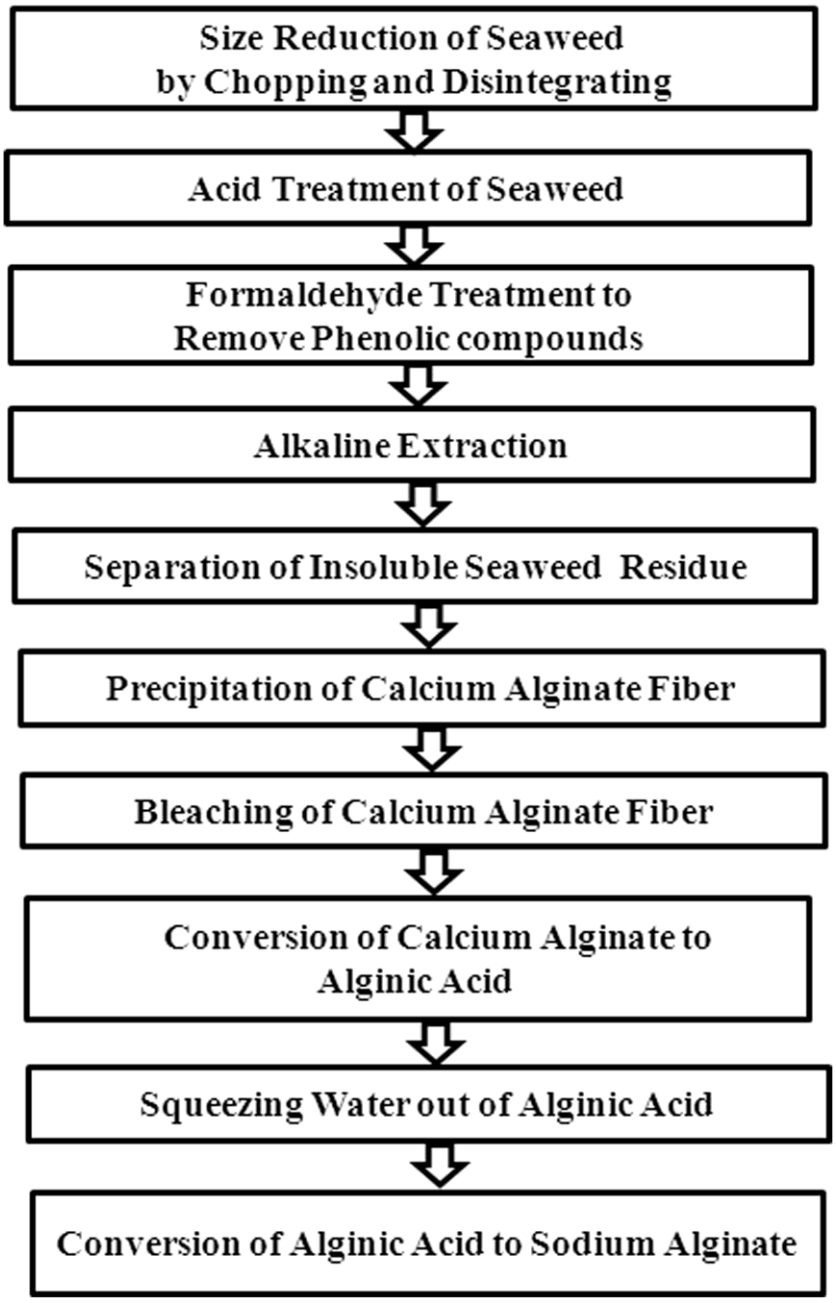


Figure 1. Schematic illustration of the calcium alginate extraction process for sodium alginate production adapted from McHugh *et al*..[54]

Step 1. Size reduction of seaweed

Dry or wet seaweed is first chopped into small pieces, and then further broken down into a slurry of seaweed and water. Water in the slurry can be separated using a centrifuge or a rotary drum screen. Seaweed having a reduced size can be transported more readily by pumping it as a slurry in water. Seaweed harvested at different times or locations could vary in both molecular weight and chemical composition of sodium alginates. Further, methods used to dry the seaweeds could lead to variations in molecular weight of sodium alginates.

Step 2. Acid treatment

The major aim of the extraction processes is to convert calcium alginate into sodium alginate. If the seaweed is treated with alkali (usually sodium carbonate) then the process necessary for extraction is an ion exchange. However, it has been demonstrated that a more efficient extraction is obtained by first treating the seaweed with dilute mineral acid: [56]

1. Pre-extraction (Alg = alginate):

$$Ca(Alg)_2 + 2H^+ \rightarrow 2HAlg + Ca^{2+}$$

2. Extraction:

$$HAlg + Na^+ \rightarrow NaAlg + H^+$$

In the pre-extraction, the calcium alginate is converted to alginic acid, which has been shown to be more readily extracted by alkali than the calcium alginate. The following extraction step can even be completed at a pH < 7.[56] Furthermore, the treatment of seaweed with the mineral acid removes the acid-soluble phenolic compounds. There are two advantages of removing phenolic compounds: (1) phenolic compounds can form brown oxidation/polymerization products with alkali and are largely responsible for a

brown discoloration which occurs during alkaline extraction, (2) phenolic compounds can cause a loss of viscosity of alginate during alkaline extraction. As a result, pretreatment (before alkaline extraction) of the seaweed with the mineral acid leads to a more efficient extraction, a less colored product, and reduced loss of viscosity during extraction.

In practice, the seaweed slurry obtained from the first step is stirred with 0.1M sulfuric acid or hydrochloric acid for 30 min in the temperature range from room temperature to about 50°C. Subsequently, the slurry of seaweed and acid can be separated on a rotary drum screen. In this step, variations in the type and concentration of mineral acid, time, and temperature could lead to different degree of molecular chain breakdown, and hence variations in molecular weight of the final sodium alginate product.

Step 3. Formaldehyde treatment

Formaldehyde reacts with phenolic groups to form insoluble products. Thus, formaldehyde, in addition to acid, is used to remove phenolic compounds from the seaweed. In practice, the seaweed slurry from step 2 is stirred with water containing 0.1-0.4% commercial formalin solution for 15-30 min at room temperature. After treatment, the seaweed is separated using a rotary drum screen and the solids are used in the alkaline extraction. The concentration of formalin solution, time of treatment, and temperature could have effect on the physical and chemical properties of sodium alginate molecules by altering the uronate monomer conformation into open structure.[57]

Step 4. Alkaline extraction

The purpose of this step is to convert the insoluble alginic acid to a soluble form so that it can be removed from the rest of the seaweed. The viscosity of the final product can also be controlled in this step by adjusting the temperature and extraction time. Higher temperature and longer extraction time result in breakdown of polymer chains and consequently lower the solution viscosity of the extracted sodium alginate. Sodium carbonate is usually used as the alkali because of its low cost.

In practice, solid contents from step 3 are stirred in a tank with the sodium carbonate solution (about 1.5%) at temperatures from 50-95°C for 1-2 h. The time can be reduced by using higher temperatures, usually with some loss of viscosity in the final product. The balance of high temperatures versus time can be used to control the molecular weight and viscosity. Meanwhile, variations in molecular weight of sodium alginate could be introduced in this step due to different temperature and processing time.

Step 5. Separation of insoluble seaweed residue

A. Flotation

The dissolved sodium alginate from Step 4 needs to be separated from the alkali-insoluble seaweed residue, which is mainly cellulose. Majority of the insoluble residue is usually removed by a flotation process. The extract dispersion from Step 4 is first diluted with 4-6 times its volume of water, to produce a suitable viscosity range, ~25-100 mPa·s. A small quantity of flocculant is added to the diluted dispersion and air is subsequently forced into the dispersion for several hours. The flocculant binds the fine particles together into large flocs, which air bubbles are more likely to attach to and lift. Since the cellulose residue is generally negatively charged, cationic flocculants are usually used, *e.g.*, the polyacrylamides. The floated flocs can be scraped from the surface and the

clarified liquid beneath will be drawn off. The dilution of the original alkali extract is necessary to yield a low viscosity which allows the particle flocs to rise within an acceptable processing time. This flotation method is a very economical and effective way of clarification but the resulting solution might be still cloudy. For pharmaceutical grade alginates, a subsequent filtration step is usually required to further remove the insoluble residuals.

In practice, dilution of the alkali extract and addition of flocculant is usually done by in-line mixing. The air can be pumped into the mixture further down the same line. The diluted, aerated extract dispersion is then pumped into large holding tanks. In a continuous process, the residual flocs can be continually scraped from the surface as the clarified liquid beneath is removed from the lower part of the tank. In a batch process, many holding tanks are used and the clarified liquid is usually drawn off near the bottom of the tank.

B. Filtration

Any insoluble residue remaining after flotation will be filtered through a rotary precoat vacuum filter, usually 2-3 cm layer of perlite. During filtration, a blade on the rotary filter continually removes the top surface of the precoat, so that a clean filter surface is always available. A new layer of precoat is usually required after 9-10 h, since most of the precoat has been removed by the scraper. For a very high clarity final product, a second filtration is sometimes used.

Step 6. Precipitation of calcium alginate

After flotation and filtration, sodium alginate needs to be recovered in solid form from its aqueous solution. Evaporation is not practical since the solution is too dilute. The alginate can be precipitated as its calcium salt or as alginic acid, either of which will later be converted to sodium alginate. In this process, calcium alginate is precipitated.

Calcium alginate can be precipitated in the form of fibers by carefully adding sodium alginate solution to a calcium chloride solution. The resultant calcium alginate fibers can be readily separated on a metal screen, and washed with water. Some seaweed give better fibrous calcium alginate than others, *e.g.*, *Laminaria* gives long fibers which are easier to handle than the short fibers obtained from *Ascophyllum*.

In practice, it is necessary to add the clear liquid obtained from Step 5 to the calcium chloride solution (about 10%) to form fibers. A suitable degree of mixing needs to be determined since too little mixing will result in a gel-type precipitate while too much mixing may cause excessive breaking up of the fibers, which are difficult to be retained on the metal screen used for separation. The precipitation may be done batch-wise in tanks or continuously using an in-line mixer.

Step 7. Bleaching of calcium alginate fiber

Bleaching can be used to improve the color and odor of the final product. It is better to perform bleaching at this stage since calcium alginate is more resistant to degradation (loss of viscosity) than alginic acid. In practice, a sufficient quantity of sodium hypochlorite solution (usually 12%) is added to a suspension of the calcium alginate fibers in water. When a suitably colored solid is obtained, the solid is again separated on a metal screen. This step could add variation to the molecular weight of sodium alginate due to oxidation of uronate monomers.

Step 8. Conversion of calcium alginate to alginic acid

In this step, calcium alginate fibers are converted into fibrous alginic acid which can be readily separated and dewatered. This is achieved by stirring calcium alginate fiber suspension in a dilute mineral acid, such as HCl. The type of acid, acid concentration, time of processing, and temperature will influence the molecular weight of sodium alginate.

Step 9. Squeezing water out of the alginic acid

A screw press is often used for the squeezing and dewatering of the fibrous alginic acid. The main advantage of this extraction process is that water can be squeezed from the resulting fibrous alginic acid more easily than the gel type of alginic acid which results from addition of acid to sodium alginate solution in the alginic acid process.

Step 10. Conversion of alginic acid to sodium alginate

After the previous nine steps, the sodium alginate from the original alkaline extract has now been purified and concentrated in the form of solid alginic acid. In this step, solid alginic acid will be converted to solid sodium alginate.

In practice, the fibrous alginic acid, usually containing greater than 25% solids, is mixed with solid alkali, normally sodium carbonate, in a mixer suitable for blending heavy pastes. Sodium alginate forms and dissolves into solution in the small amount of water present, resulting in a heavy paste. The neutralization process can be readily controlled to obtain homogeneous final product. The reaction can be heated to 50°C. The formed heavy paste is forced through small holes and the extrusions are chopped into pellets. The pellets are subsequently dried either on trays in a hot-air oven or in a fluid-bed dryer on a large scale. A fluid-bed dryer fitted with a vibrating tilted screen is

usually used so that the pellets, continuously fed in, can vibrate down the screen and out, as the hot air blows up through the screen. The dried pellets (about 10% moisture) can be milled to an appropriate particle size to achieve the final solid sodium alginate. The processing variables in this final step could lead to variations in molecular weight of sodium alginate.

In summary, it generally takes ten steps to extract sodium alginate from the seaweed. It is obvious that, in addition to the variations of the source materials, variations in chemicals and process parameters used in the extraction steps could result in variations in chemical composition and molecular weight of the final sodium alginate products. Different manufacturers may use different steps to extract sodium alginate from seaweed and hence produce sodium alginate varying in chemical composition and/or molecular weights. Even for the same manufacturer, batch-to-batch variability could be expected due to the variations in the processing steps.

Physicochemical Properties of Sodium Alginate

Sodium alginates are linear, unbranched, amorphous polysaccharides. They are copolymers of β-D-mannuronate (*M*) and α-L-guluronate (*G*) linked to each other by 1→4 glycosidic bonds. The *M* and *G* units in the alginates may be randomly or non-randomly arrayed as heterogeneous or homogeneous sequences (Figure 2). In homogeneous *G* sequences, the *G* units are linked together by diaxial glycosidic bonds (glycosidic bond is at axial position at both 1 and 4 carbon in the adjacent gluronic acid monomers) to form a buckled chain. Due to intra-molecular hydrogen bonding and steric hindrance between adjacent *G* units, homogeneous *G* sequences usually exhibit an extended, less flexible structure in solution.[58-60] In homogeneous *M* sequences, the

mannuronic residues are connected by diequatorial glycosidic bonds (glycosidic bond is at equatorial position at both 1 and 4 carbon in the adjacent mannuronic acid monomers), forming a flexible ribbon-like structure due to a decrease in both steric hindrance and intra-molecular hydrogen bonding. Heterogeneous *M*-*G* sequences contain both equatorial-axial and axial-equatorial linkages and the differing degrees of freedom of the two residues result in greater overall flexibility than for (1→4)-linked-β-D-mannuronate chains. Hence, the stiffness of the chain sequences increases in the order: *MG* < *M* < *G*.[58-60]

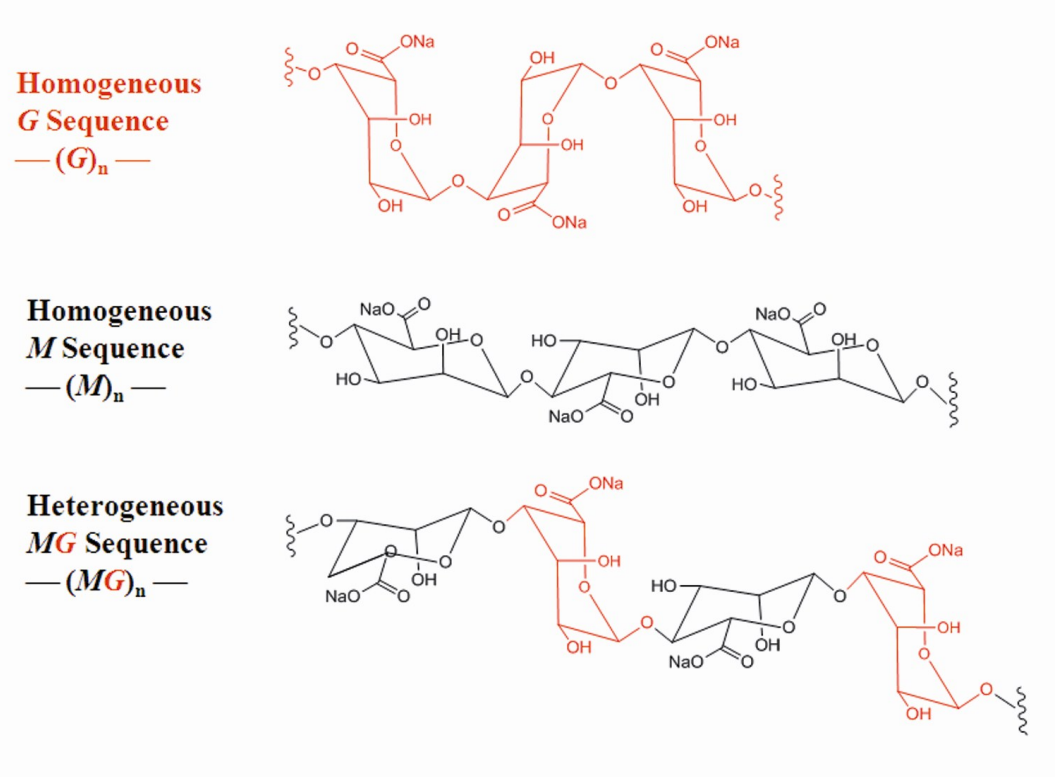


Figure 2. Sodium alginate sequences (from top to bottom): homogeneous *G* sequence, homogeneous *M* sequence, and heterogeneous *M*-*G* sequence. *G* is short for guluronate, while *M* represents mannuronate.

Alginates exist as a matrix polysaccharide in seaweed, comprising up to 40% of the dry weight of seaweed. Different species of seaweed have different habitats that expose them to periodic drying due to tidal patterns and waves, which lead to the differences in plant stiffness and elasticity. The stiffness and elasticity of seaweed is controlled by the chemical composition and sequence distribution of alginate. Therefore, the properties of alginates depend on the seaweed species from which sodium alginate is extracted.

The physical properties of alginates are closely related to the chemical composition.[61-63] For example, the solubility of alginate in acid is correlated with the proportion of *MG* sequence. The formation of calcium alginate gels involves the homogeneous *G* sequence, so sodium alginate with higher proportion of *G* sequence usually form calcium alginate gels with greater gel strength.[64-66] Thus, it is important to determine the relative proportions of the uronic acids of alginates. Various methods have been developed to measure the ratio of mannuronate to guluronate (the M/G ratio) in alginates.[58,63,67-69] Chemical compositions for sodium alginate extracted from some common seaweed species are listed in Table 1.[70]

Table 1. Fractional chemical composition of sodium alginates extracted from various seaweed.[54]

Source	***G***	***M***
Ascophyllum nodosum (old tissue)	0.36	0.64
Ascophyllum nodosum (fruiting bodies)	0.10	0.90
Durvillea antartica	0.29	0.71
Laminaria digitata	0.46	0.54
Laminaria hyperborea (Stipe)	0.68	0.32

Laminaria hyperborea (Leaf)	0.55	0.45
Laminaria hyperborea (outer cortex)	0.75	0.25
Laminaria japonica	0.31	0.69
Macrocystis pyrifera	0.39	0.61

The determination of the sequence distribution would be more useful, but also more difficult to obtain. By using a solution NMR method, it is possible to determine the percentage of each monomer (*G* or *M*), each of the four possible dimers (*GG*, *MM*, *GM*, and *MG*), and possibly each of the eight trimers (*GGG*, *MMM*, *GGM*, *GMM*, *MGG*, *MMG*, *MGM*, *GMG*).[69,71] However, it is still not possible to determine the exact distribution of the three sequences.

The M/G ratio of alginate can be modified, on a laboratory scale, by treating it with "mannuronan C-5 epimerase," an enzyme isolated from the soil bacterium, *Azotobacter vinelandii*.[66,72] This enzyme converts mannuronic acid residues into guluronic acid residues in the polymer chain, and the resulting alginate forms stronger gels.[66,72] However, application of enzyme modification of alginates on a large scale was limited due to the low production of this enzyme by bacterial culture and its low stability under operational conditions.[63]

Pharmaceutical Application

Sodium alginates have wide applications in the pharmaceutical and biomedical areas due to their abundance, low price, and compatibility with biological systems. Pharmaceutically, sodium alginates are generally used as binding agents in tablets, as suspending and thickening agents in suspensions, water-miscible gels, lotions and creams, as emulsion stabilizers, or as gel-forming agents in combination with divalent metal ions such as calcium.[30] Of particular interest is their potential in the development of alginate-based controlled release drug delivery systems.[29]

In the development of a peroral controlled-release drug delivery system, the dosage forms are often prepared according to two designs: 1) the entire drug dose is contained in the same physical unit (matrix design); 2) the dose is contained in an assembly of small sub-units, which are subsequently filled into a capsule or compressed into a tablet. The controlled release of the drug is achieved by the formation of a barrier around the formulations. Several formulation techniques can be used to incorporate the barrier into the peroral drug delivery systems, *e.g.*, the inclusion of active pharmaceutical ingredients (APIs) in a polymer matrix, or the application of coating of a core containing the APIs. Sodium alginate can play a significant role in the design of a controlled-release drug delivery system, owing to the fact that sodium alginate undergoes almost immediate hydration to create a viscous layer, which subsequently decreases the diffusion rate of drug molecules.

When alginate-based matrix systems are exposed to an aqueous dissolution medium, drug release is modulated by diffusion through the swelling matrix and by dissolution/erosion of polymer gel at the gel/water interface. Water-soluble drugs are

released primarily by diffusion of dissolved drug molecules across the viscous gel layer, while poorly water-soluble drugs are released predominantly by erosion mechanisms. Alginate-based matrices have been employed to prolong release of many drugs including ibuprofen, theophylline, chlorpheniramine maleate, pseudoephedrine hydrochloride, and acetyl salicylic acid.[31,73-77] In addition, previous studies have demonstrated the feasibility of preparing alginate matrix tablets industrially.[76,78]

The pH of the dissolution medium plays an important role in the drug release profile from alginate-based matrices. Sodium alginate reacts with H^+ to form insoluble alginic acid in gastric fluid (pH 1-3). On the other hand, sodium alginate forms a viscous solution in intestinal fluid (pH 6-7). As a result, water-soluble drugs diffuse through the alginic acid gel in gastric fluid and through the viscous polymer solution in intestinal fluid. Water-insoluble drugs mainly release in intestinal fluid with the erosion of sodium alginate gel and have minimal release in gastric fluid.[74] By incorporating a pH independent hydrocolloid gelling agent (*e.g.*, cellulose polymers) in the tablet the release rate of a basic drug can be made independent of pH.[79]

Sodium alginate has also been used as a coating material in the preparation of dry-coated tablets, leading to a reduced drug release rate.[73,80] Sodium alginate was applied to coat gelatin capsules, which could remain intact in the stomach due to the formation of alginic acid gel, allowing for drug delivery selectively to the intestine.[81] In addition, microspheres containing highly water-soluble drugs (*e.g.* acebutolol HCl) can be powder-coated with sodium alginate to formulation into capsules or tablets, for a prolonged drug release effect.[82]

Sodium alginate has also been used in a buoyant capsule formulation for controlled release of a basic drug.[83] In the stomach, sodium alginate forms alginic acid gel which entraps air inside the less dense powder bulk, resulting in capsule buoyancy. After buoyancy is lost, the dosage form is emptied into the intestine, where the gelled powder plug changes structure and becomes more porous as the alginic acid turns into soluble sodium salt with an increase in pH.

Sodium alginate has also demonstrated to have excellent bioadhesive properties and thus can be applied in bioadhesive formulations to extend the gastrointestinal residence time.[84] In addition, sodium alginate suspensions have shown promising effects in treating gastro-esophageal refluxate by adhering to esophageal tissue for periods up to one hour and forming a protective alginic acid gel layer against components in gastric reflux.[85,86]

Sodium alginate is also widely used as a gelling agent due to its ability to form gels with divalent cations (*e.g.*, Ca^{2+}) under mild conditions. The ionotropic gelation of sodium alginate with calcium is conventionally described by the "egg-box" model, where the divalent cations interact with guluronic acid monomers in the cavities formed by pairing up of the *G* sequences of the alginate molecular chains (Figure 3).[87,88] Recent studies on calcium alginate gel formation reveal three distinct and successive steps of calcium binding to alginate with increasing calcium concentration: 1. interaction of calcium with a single *G* monomer; 2. formation of egg-box dimers; and, 3. lateral association of dimers to form multimers.[89] The homogeneous *G* sequence percentage and molecular weight of sodium alginate determine the association modes of dimers and multimers of the resultant calcium alginate gels.[89]

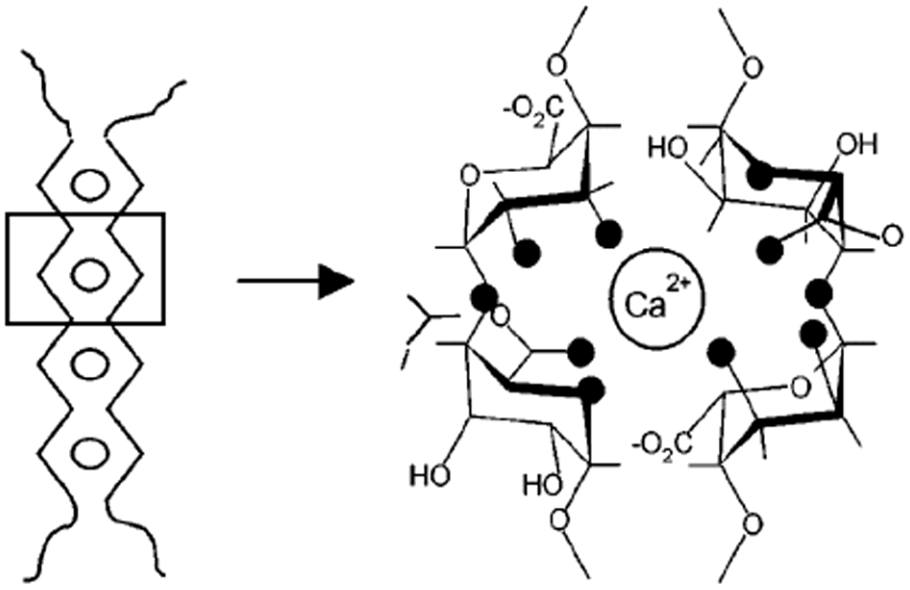


Figure 3. Illustration of the "egg-box" model for calcium alginate gel and the interaction between calcium cations and oxygen atoms (filled circles) on the guluronic acid monomers. (Reprinted from "Grant GT, Morris ER, Rees DA, Smith PJC, Thom D. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Lett 32:195-198", Copyright (1973), with permission from Elsevier).

Calcium alginate gels have been used in wound dressings, dental impressions, and controlled release drug delivery systems.[90-93] In controlled release systems based on sodium alginate cross-linked with calcium chloride, the diffusion of drug molecules are determined by the swelling and erosion behavior of calcium alginate gels. Under acidic conditions (*e.g.*, in the stomach) with pH < pKa of alginic acid, swelling of the calcium alginate gels rarely occurs. Drug molecules are likely to be released by diffusion through the insoluble gel matrix. Under conditions with pH > pKa of alginic acid (*e.g.*, in the

intestine), the calcium cations in alginate gels, even those bound with the homogeneous G sequence, can be displaced by monovalent cations at high salt concentration (*e.g.,* > 0.2 M Na^+), resulting in an increased swelling and erosion.[94]

It has been shown that higher alginate concentrations[95,96] and higher guluronic acid percentage[95,97] lead to a slower drug release rate from calcium alginate gel beads. Sodium alginate rich in guluronic acid tends to form more rigid gels that are less prone to swelling and erosion since the homogeneous *G*-sequences have a high degree of coordination of the calcium cations.[64-66] Drug release from calcium alginate gel beads is also influenced by the interaction between drug molecules and the alginate. For example, gentamicin sulfate was found to interact with the mannuronic acids of alginate without influencing the gelation of alginate with calcium ions. As a result, calcium alginate beads prepared from sodium alginate with a higher mannuronic acid content led to a slower release of gentamicin sulfate.[98]

Higher calcium concentration[95,99] and a longer gelling time during the preparation process of calcium alginate beads[95,99] result in slower drug release profile. The cross-linker type has been shown to have a pronounced influence on the drug release:[100] calcium alginate beads demonstrated more prolonged drug release profiles than alginate beads prepared from other cross-linking agents like Ba^{2+} and Sr^{2+}. Calcium alginate beads with various sizes have been applied to achieve a pulsatile drug delivery pattern for dextran.[101] Thus, calcium alginate beads can be designed to change the release time onset and used as drug delivery systems intended to follow the circadian rhythm in the body.

Calcium alginate gel can be formed at neutral pH and isotonic solution at room or body temperature. As a result, calcium alginate gel can be used as a matrix for the

entrapment and/or delivery of biomolecules, such as proteins, DNA, and live cells without deleterious effect on their three-dimensional structure and/or biological activity.[102-104] The porosity of the gel can be adjusted to allow for acceptable diffusion rates of macromolecules or small molecules.[105]

A large number of proteins have been encapsulated in alginate microbeads, such as basic fibroblast growth factor, Interleukin-2, Leukaemia inhibiting factor, lactase, *etc*.[106-108] Positively charged proteins (*e.g.*, transforming growth factor-b) can potentially compete with calcium ion for available carboxylic acid sites on the alginates, leading to protein inactivation or a reduction in diffusion rate. In this case, additives (*e.g.*, polyacrylic acid) can be included to protect the encapsulated protein from the alginate.[109]

Protein (bovine serum albumin) diffusion within calcium alginate gels was found to depend on the chemical composition of sodium alginate: gels prepared from sodium alginate of lower guluronic acid content showed higher protein diffusion rate than gel prepared from sodium alginate with similar viscosity but higher guluronic acid content.[110] Furthermore, alginate-based microencapsulation of living cells, such as islet cells, for transplantation has been widely investigated and has shown promising results in both animal studies and clinical trials.[104,111]

Recently, FMC Biopolymer developed a novel alginate capsule technology based on calcium alginate gel formation. In this technology, calcium alginate gel capsules are prepared as unique enteric non-gelatin softgel capsules, particularly suitable for the delivery of large dose actives, acid sensitive active or actives generating gastric irritation, and oxygen sensitive actives. Alginate softgel capsules are produced by the following process: 1), emulsions containing actives (oil phase), and $CaCl_2$ (gelling salt) are

prepared; 2), emulsions are dropped into sodium alginate solution to form calcium alginate gel shell; 3), alginate softgel capsules are washed and dried. Alginate softgel capsules have the following advantages over conventional gelatin softgel capsules: thinner films (100-150 μm), low variability in film thickness, seamless technology, smaller size, and excellent dosage uniformity (1-3% relative standard deviation).

Characterization

More than 200 different alginate grades varying in molecular weight and chemical composition are available from manufacturers.[29] The heterogeneity of commercial pharmaceutical-grade alginates reflects differences among the botanical sources, seaweed harvesting locations, the season of harvesting, the plant parts employed, and the processing methods used. Current pharmacopoeial standards (USP 33-NF28) for sodium alginate include the following specifications and tests (Table 2):

Table 2. Compendial specifications for sodium alginate (Sodium alginate monograph, USP34 – NF29).

Test	USP-NF
Identification*	+
Microbial limits	≤ 200/g
Loss on drying	≤ 15.0%
Ash	18.0-27.0%
Arsenic	≤ 1.5 ppm
Lead	≤ 0.001%
Heavy metals	≤ 0.004%
Assay (dried basis)	90.8-106.0%

*Qualitative determination of the existence of sodium alginate by forming gel with calcium cations or with addition of sulfuric acid.

However, these specifications and tests do not enable the characterization of variations in the molecular weight distribution and/or chemical composition of sodium alginate. As these variations can markedly affect the processability or performance of a sodium alginate-containing pharmaceutical product,[31,32] it is important to find effective methods to characterize sodium alginate.[1]

The American Society for Testing and Materials (ASTM) standard test methods for sodium alginate recommend using size exclusion chromatography with multi-angle laser light scattering detection (SEC-MALS) for the determination of molecular weight distribution. H^1 solution NMR has also been employed to characterize the chemical composition of such excipients. However, both methods are time-consuming and the results are not directly indicative of the functionality of sodium alginate in formulations.

An effective method of excipient characterization should reflect the excipient's behavior during processing and its functionality in potential formulations. Sodium alginates are mostly used as binders, thickeners and gel-forming agents in both conventional and controlled release formulations. The functionality of sodium alginate in these formulations can be related to its rheological behavior in aqueous solutions. Rheological behavior of polymers in solution is influenced by the molecular weight distribution of a polymeric mixture.[112-114] Furthermore, rheological parameters are closely related to pharmaceutical processes and functionality. For instance, viscosity is an important factor contributing to sedimentation rate of suspensions or emulsions as described by the Stokes' law for particle sedimentation velocity:[115,116]

$$V = \frac{2(\rho_{particle} - \rho_{fluid})r^2 g}{6\pi\eta}, \qquad \text{Equation 1}$$

where V is the sedimentation rate (m/s), ρ is the density (kg/m^3), r is particle radius (m), g is gravitational acceleration (m/s^2), and η is the fluid viscosity (Pa·s). Viscoelasticity is another important property of polymer solutions, reflecting the extent of polymer-solvent interaction and polymer interchain association, aggregation, and entanglement.[117] A polymer solution with high apparent viscosity and viscoelasticity may exhibit excellent suspending properties by trapping the dispersed particles in the quasi-gel network.[117]

Viscosity also plays an important role in the solute diffusion and dissolution in viscous environment as described by Stokes-Einstein Equation on Diffusivity and Noyes-Whitney equation on solute dissolution.

$$D = \frac{k \cdot T}{6\pi r \eta}, \qquad \text{Equation 2}$$

Where D is diffusivity, k is Boltzmann's constant, T is temperature in Kelvin, r is particle radius, and η is fluid viscosity.

$$\frac{dM}{dt} = D \cdot A \cdot \frac{C_s - C_b}{h} = \frac{kT}{6\pi r \eta} \cdot A \cdot \frac{C_s - C_b}{h}, \qquad \text{Equation 3}$$

where M is the mass dissolved, t is time, A is the surface area of solute particle, C_s is the solubility of the solute, C_b is the bulk solution concentration of the solute, and h is the thickness of diffusion layer.

In the case of alginate-based matrices, sodium alginate swells to forms a hydrated polymer layer when it is in contact with water, resulting a typical polymer concentration and polymer entanglement profile in the hydrated polymer matrix as shown in Figure 4, where x is the distance from the unhydrated polymer surface. [118,119]

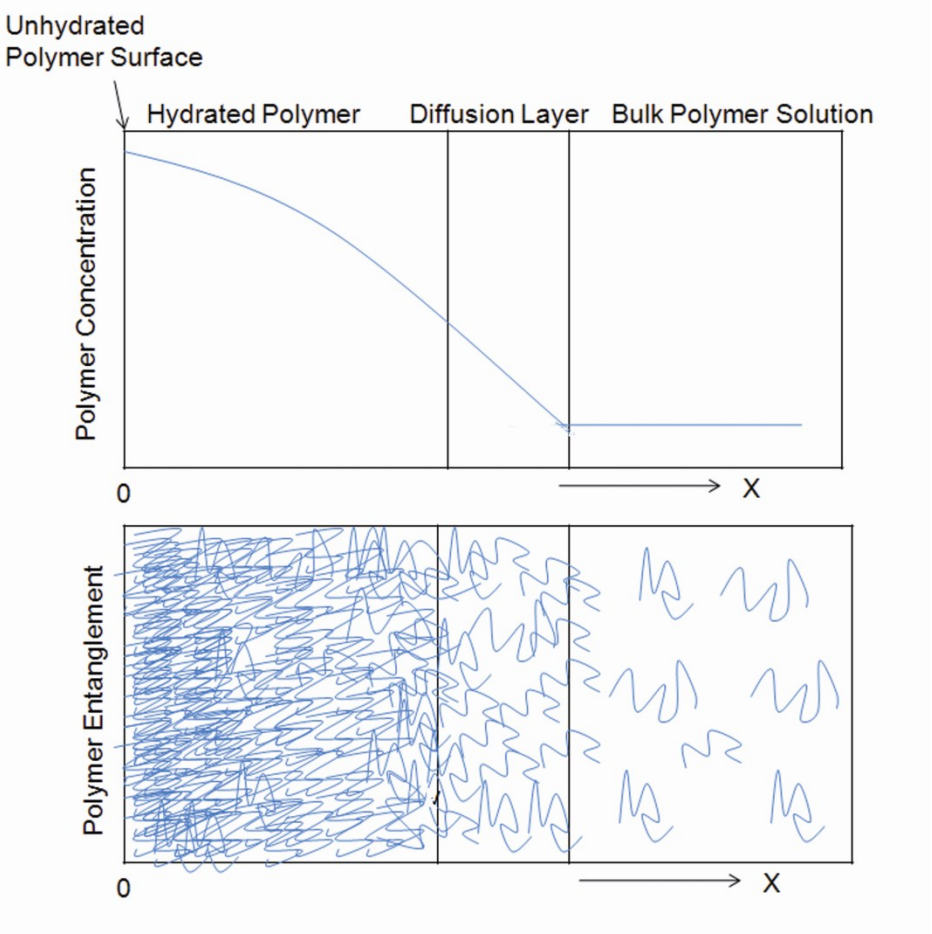


Figure 4.Schematic illustration regarding the polymer concentrations and polymer chain entanglement in swelling matrix.

Drug release initially starts from the surface of the matrices, followed by drug diffusion through, and/or erosion of the hydrated sodium alginate layer. Erosion of the hydrated layer is the result of the disentanglement and dissolution of alginate chains at the interface between the polymer gel and the bulk solution.[118] It is very likely that erosion of the alginate hydrated layer is governed by the same polymer-solvent and polymer interchain interactions as those involved in rheological behavior.[120] Viscoelastic parameters of other hydrophilic polymer solutions (*e.g.*, hypromellose) were found to correlate with the erosion of polymer gels: *i.e.*, the higher the elastic modulus, the slower

the erosion rate of gel.[121,122] As a result, viscoelasticity of sodium alginate in the hydrated state is also expected to play an important role in the swelling and erosion behavior of matrices in water, and eventually the drug release profile from alginate-based matrices. Therefore, rheological methods could be applied to characterize sodium alginate in solution.

RHEOLOGY

Rheology is the science of deformation and flow of matter and the study of the manner in which materials respond to the applied stress or strain. Rheological principles stem from two fundamental laws: Hooke's law of elasticity and Newton's law of flow. These laws correspond to the two extremes of rheological behavior, *i.e.*, elastic deformation and viscous flow, respectively. Elastic or Hookean deformation involves material under stress that returns to its original state when the stress is removed. Viscous or Newtonian flow means that a fluid undergoes flow with the application of the smallest stress and does not return to its original state when the stress is removed.

Elastic deformation is described by Hooke's law as:

$$E = \frac{\sigma}{\varepsilon}, \qquad \text{Equation 4}$$

where E is modulus of elasticity (Pa), σ is stress (Pa), and ε is strain.

Simple shear flow of viscous liquid between two parallel plates is the continual movement of hypothetical layers of liquid sliding over each other as shown in Figure 5.

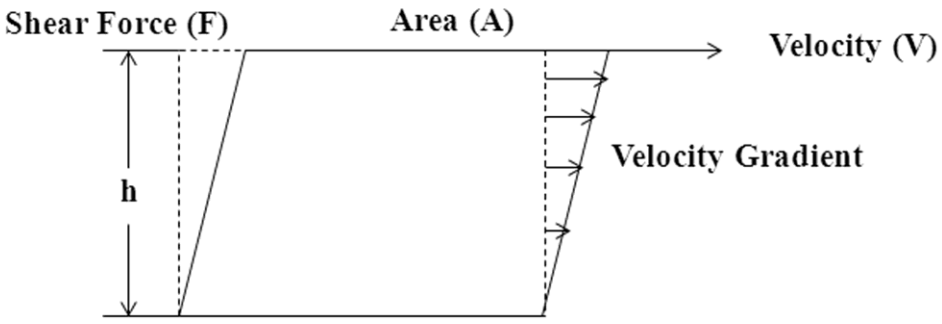


Figure 5. Velocity profile under shear flow between two parallel plates.

In the simplest case the velocity of each layer increases linearly with respect to the distance from the lower stationary plate. The gradient of the velocity in the direction at right angles to the flow is called the shear rate ($\dot{\gamma}$), and the force per unit area created or produced by the flow is called the shear stress (σ). In this simple case, the shear rate is *V/h*, while the shear stress is given by *F/A*. The shear viscosity is the resistance to flow of a liquid and is defined according to Newton's law as:

$$\eta = \frac{\sigma}{\dot{\gamma}} \qquad \text{Equation 5}$$

Simple liquids follow Newton's law and their viscosity is independent of the shear rate. These are classified as Newtonian liquid, of which water is an example. Other liquids show decreased or increased viscosity with the increase of shear stress or shear rate, and are classified as shear-thinning or shear-thickening non-Newtonian liquids, respectively (Figure 6).

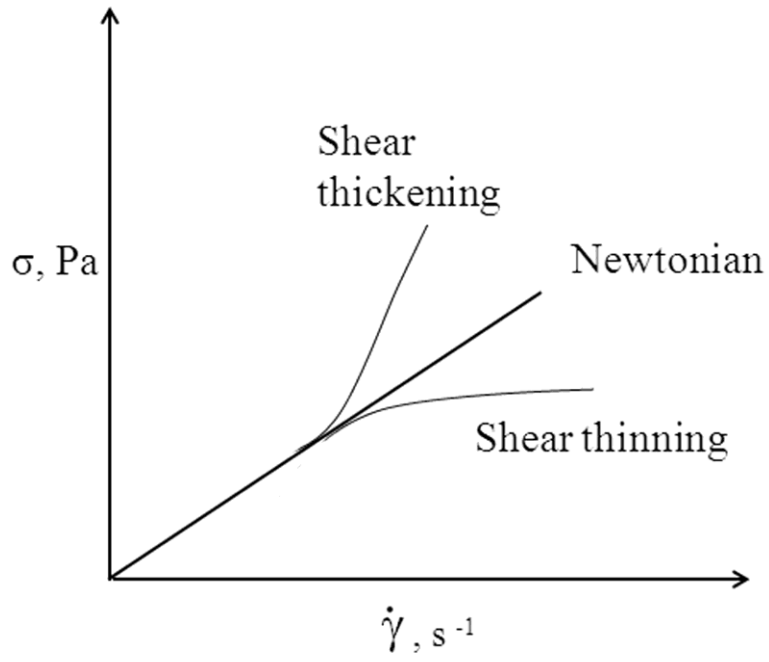


Figure 6. Shear behavior of Newtonian and non-Newtonian liquids.

The shear stress-shear rate relationship for the different types of liquids can be described as:

$$\dot{\gamma} = k \cdot \sigma^n \qquad \text{Equation 6}$$

where k is constant and $k > 0$, $n = 1$ for Newtonian liquid, $0 < n < 1$ for shear-thickening liquid, and $n > 1$ for shear-thinning liquid.

Most polymer solutions are shear-thinning liquids. Characteristic shear rates related to pharmaceutical processing and application are listed in Table 3. The apparent viscosities as a function of shear rate for the non-Newtonian liquids are usually determined by steady shear method.

Table 3. Typical shear rates for pharmaceutical operations.[35,123]

Operation	**Shear rate, s^{-1}**
Fine Particle Sedimentation	~ 10^{-3}
Coatings Draining off Surface under Gravity	10^{-1} – 10^{1}
Pouring liquid from bottle	50
Extrusion	1–100
Pumping (Pipe Flow or Blood Flow)	1-3,000
Mixing and Stirring	10 – 1,000
Spreading Lotion/Cream on Skin	400 – 1,000
Levigating Ointment using Spatula	400 – 1,000
Injecting through Syringe	4,000
Dispersing Nasal Spray	20,000
Processing in Colloid Mill	10^{5} – 10^{6}
High-speed Coating	10^{4} – 10^{6}
Spray Drying	10^{5} – 10^{6}

Most materials/liquids encountered in pharmaceutical practices do not exhibit ideal behavior as described by Hooke's law or Newton's law. Those liquids that simultaneously exhibit fluid-like (viscous) and solid-like (elastic) behavior are named as viscoelastic materials. The viscoelasticity of a material can be measured using the small amplitude oscillation method, where the material is subjected to sinusoidal strain input

and the stress response is measured. Materials are generally tested in the 'linear viscoelastic region', where the inner structure of the material is not destroyed by the input strain and the material's response to sinusoidal input is also sinusoidal with the same frequency.

The phase shift (δ) between the input strain and output stress and their amplitude reflects the viscoelastic behavior of the material (Figure 7). For an ideal elastic solid material, the applied force induced by the application of strain is transmitted through the sample quickly, and changes in stress are observed at nearly the same time as the applied strain. Thus, δ would be zero. For an ideal viscous fluid, δ is 90°. For a viscoelastic material, the stress and strain are out of phase and δ is between 0° and 90°.

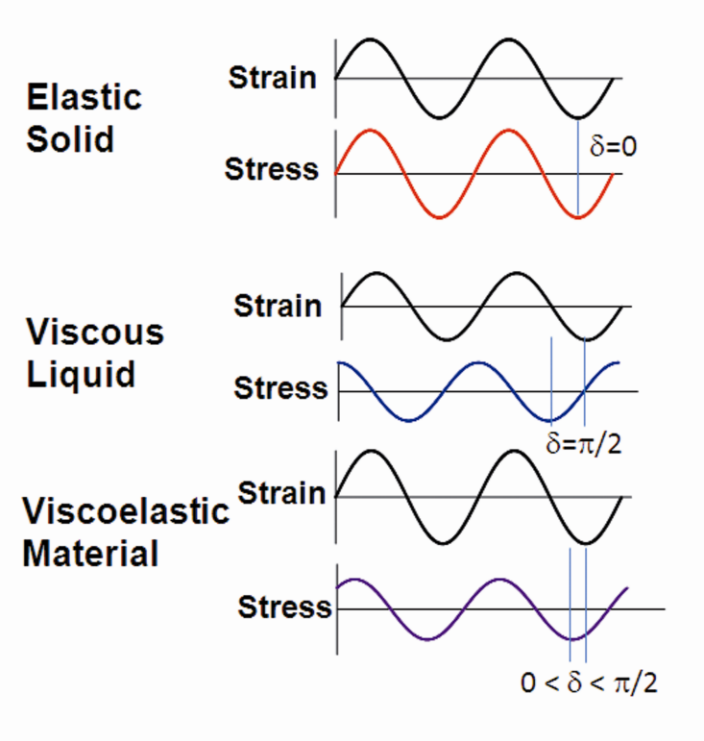


Figure 7. Phase shift (δ) for different fluids(from top to bottom): elastic solid, viscous fluid, and viscoelastic material.

For an oscillatory shear flow, the shear stress σ and shear strain γ oscillates with a

frequency of oscillation ω as:

$$\gamma = \gamma_0 \sin(\omega t), \qquad \text{Equation 7}$$

$$\sigma = \sigma_0 \sin(\omega t + \delta), \qquad \text{Equation 8}$$

Shear stress with oscillation can be expressed as:

$$\sigma = \sigma' + \sigma'' = \sigma_0' \sin(\omega t) + \sigma_0'' \cos(\omega t), \qquad \text{Equation 9}$$

Elastic or storage modulus is defined as the ratio of the in-phase stress with the strain.

$$G' = \frac{\sigma_0'}{\gamma_0} = \frac{\sigma_0}{\gamma_0} \cos\delta, \qquad \text{Equation 10}$$

Loss modulus (G″) is defined as the component of stress 90° out-of-phase with the strain.

$$G'' = \frac{\sigma_0''}{\gamma_0} = \frac{\sigma_0}{\gamma_0} \sin\delta, \qquad \text{Equation 11}$$

The measure of the viscous/elastic ratio of the viscoelastic material is the ratio of G″ to G′ and is defined as loss tangent:

$$\tan\delta = \frac{G''}{G'}, \qquad \text{Equation 12}$$

From a molecular point of view, elasticity of polymer solutions is attributed to the entanglement and relaxation of polymer chains.[124] Rheologically, polymer gels are often distinguished from polymer solutions on the basis of the timescale dependence of the elasticity and viscosity as reflected in dynamic moduli: G′ and G″. An example is a semidilute polymer solution, in which polymer chains entangle with each other. For this kind of solution, G′ < G″ at low frequencies since those chains have sufficient time to

disentangle and flow during a single oscillation; and G′ > G″ at high frequencies due to the insufficient time for polymer chains to disentangle during a single oscillation, and thus the system appears as solid.[125] Therefore, the lifetime or the relaxation time of the polymer entanglements determines whether the system appears a solid or a liquid in the mechanical spectrum in the available angular frequency range. When the lifetime of the interchain entanglements is sufficiently longer than the time scale of observation (1/ω), a solid-like mechanical spectrum is obtained. And the crossover frequency at which G′ equals G″ corresponds to the average relaxation time of entanglements.[33] Thus, a gel should exhibit a solid-like mechanical spectrum, *i.e.*, G′ > G″ throughout the experimentally accessible angular frequency.[33]

Rheometers

The Ubbelohde capillary viscometer is usually used for the determination of intrinsic viscosity (Figure 6) based on Poiseuille's law:

$$\frac{dV}{dt} = \frac{\pi r^4}{8\eta} \cdot \frac{\Delta P}{L} = \frac{\pi r^4}{8\eta} \cdot \frac{\rho g \Delta h}{L}, \qquad \text{Equation 13}$$

where V is the volume of the liquid (L), t is time (second), r is internal radius of the tube (m), L is the length of the tube (m), ΔP is the pressure drop (Pa), and η is the dynamic viscosity (Pa·s). Usually the viscosity of a polymer solution is compared to the solvent, where the relative viscosity is given by:

$$\eta_r = \frac{\eta_{solution}}{\eta_{solvent}} = \frac{t_{solution}\rho_{solution}}{t_{solvent}\rho_{solvent}}, \qquad \text{Equation 14}$$

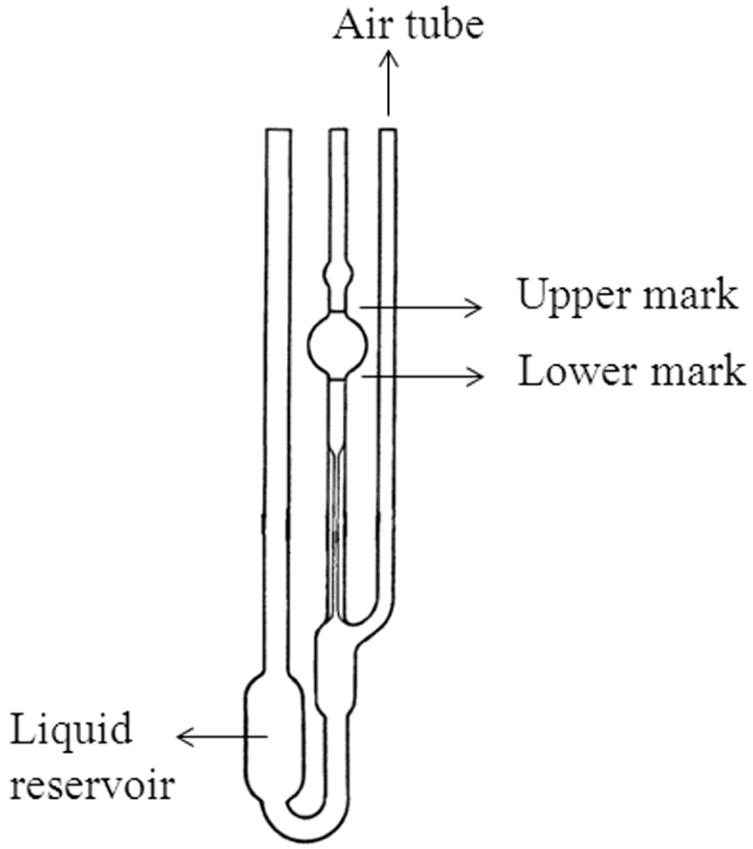


Figure 8. Ubbelohde capillary viscometer ((Reprinted from "Aulton M. E., Pharmaceutics The Science of Dosage Form Design 2nd Edition", Copyright (2001), with permission from Elsevier).

The AR 2000 rotational rheometer (TA instruments, New Castle, DE, USA) equipped with cone-and-plate is used for the steady shear and small amplitude oscillation measurements in this study (Figure 9). This rheometer is an air bearing, controlled stress/controlled rate rheometer. The use of air as lubricating medium allows application of torque with very little friction. The auto zero gap setting on the instrument sets a reproducible zero gap before actual measurement. Once the sample is loaded on the plate, the gap is closed automatically using this zero gap as the reference. The Peltier effect[126] is

used in temperature control for fast and precise control. The Peltier effect is a reversible thermoelectric effect where magnitude and direction of current applied to Peltier elements can result in desired heating or cooling. The AR 2000 rheometer uses four Peltier elements which are surrounded by a heat exchanger through which water or cooling fluid can be circulated for removal of heat from Peltier plates.

Figure 9. The AR 2000 rotational rheometer (reprint from TA instruments product brochure with permission from TA Instruments, New Castle, DE, USA).

The measuring system used is the cone-and-plate accessory (40 mm in diameter and 1° cone angle with truncation of 51 μm) (Figure 10). The materials of construction used in the geometries are stainless steel. The velocity at any point on the rotating surface

(either the cone or the plate) is given by $r\omega$ where r is the distance from the center of rotation and again ω is the rotation rate in rad/s. The distance between the cone and plate at this point is given by $r \cdot tan\theta$, where θ is the angle between the cone and plate. If the cone angle is small (less than 4°), $tan\theta$ can be approximated as θ in radians. Thus, the shear rate is defined as:

$$\dot{\gamma} = \frac{r\omega}{r\theta} = \frac{\omega}{\theta}, \qquad \text{Equation 15}$$

The shear rate is therefore the same everywhere under the cone.

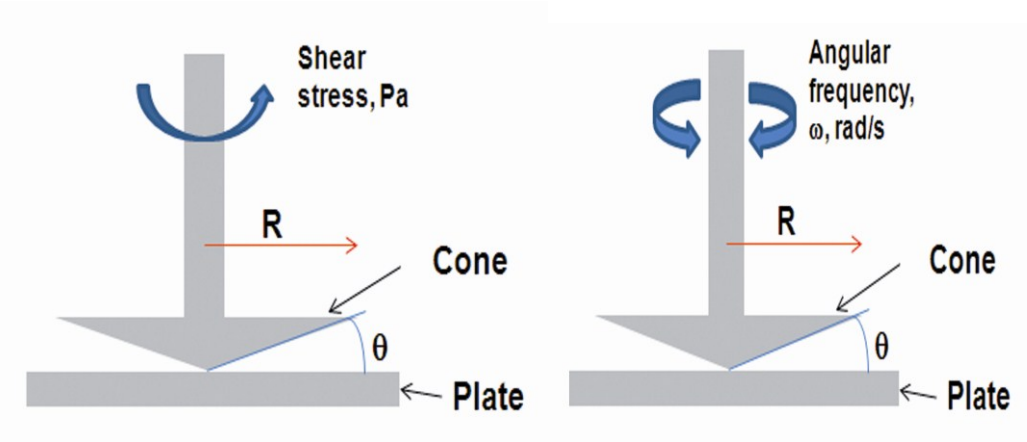


Figure 10. Illustration of AR 2000 cone-and plate: *R*: radius of the cone, and θ : angle of the cone.

Rheological Characterization of Sodium Alginate Solution

A number of studies have been published on the rheological behavior of sodium alginate solutions.[37,39-47,127-129] In 1970, Smidsrod[129] determined the intrinsic viscosities

of several sodium alginate samples with molecular weight ranging from $1x10^5$ to $2.7x10^6$ in aqueous salt solutions. The intrinsic viscosity of sodium alginate solution was found to decrease with increasing ionic strength, which was due to the fact that sodium alginate conformation became more compacted as a result of reduced intra-molecular electric repulsion.

Kokini and Surmay[124] studied the apparent viscosity of sodium alginate solutions as a function of shear rate and concentration. Sodium alginate investigated in this study was one unspecified grade obtained from Kelco (Atlanta, Georgia). Sodium alginate solutions having concentrations of 1.25%, 1.5%, 1.75%, and 2.0% w/w were characterized in the shear rate range from 0.1 to 100 s^{-1}. All solutions showed shear-thinning behavior. The steady shear behavior of sodium alginate solutions at different concentrations could be superimposed by plotting reduced viscosity (*i.e.*, apparent viscosity at each shear rate divided by zero shear viscosity) as a function of the generalized shear rate (the true shear rate multiplied by the inverse of the shear rate at which reduced viscosity is equal to 0.8). Their finding indicated that sodium alginate solutions showed the same degree of shear thinning in the concentration range investigated.

Mancini *et al.*[127] measured the intrinsic viscosity of four commercial grades of sodium alginate and their apparent viscosities in the concentration range of 0.125-1.5% at 278K to 308 K. It was reported that the investigated sodium alginate solutions showed shear thinning behavior and the apparent viscosity of sodium alginate solutions decreased at higher temperature. An empirical relationship among apparent viscosity, shear rate, and average molecular weight of sodium alginate was also proposed. However, only four

data points in the molecular weight range from 70 to 160 kDa were used to develop a rather complicated empirical relationship. Furthermore, the proposed empirical equation was not validated with additional data.

Cancela *et al.*[39] investigated the steady shear behavior of one grade of sodium alginate (high purity grade obtained from Prolabo, France) at concentrations of 0.5%, 1.0%, and 1.5% w/w in the temperature range from 25 to 40 °C. Shear-thinning behavior was observed for sodium alginate solutions at all three concentrations. Apparent viscosities of sodium alginate solutions were found to decrease with increasing temperature.

Gomez-Diaz and Navaza[128] characterized the intrinsic viscosity and steady shear behavior of one unspecified grade of sodium alginate obtained from Aldrich at concentrations from 0.1 to 0.75% w/v in the temperature range 25 – 40 °C. It was observed that sodium alginate produced a marked shear thinning effect in solution even at such low concentrations. Concentration had a positive effect on solution viscosity while temperature negatively influenced the apparent viscosities and the shear thinning behavior. Their findings are in agreement with previous studies.[124,127] These results suggested that sodium alginate chains in solution start to interact with each other at very low concentrations and the apparent viscosity of sodium alginate solutions is influenced by both shear rate and temperature at a fixed concentration. Thus, when comparing the solution viscosity data of sodium alginate from different sources, it is critical to make sure that these viscosity data were generated at the same concentration under the same shear condition and temperature.

Nikerson and Paulson[40] determined the critical overlap concentration of sodium alginate (one food grade Protanal GP 9356 from FMC) solution. Critical overlap concentration of polymer solution is the concentration below which polymer chains will not have interactions with each other in a very dilute environment. Experimentally, the critical overlap concentration was assumed to be notable by a marked increase in apparent viscosity as polymer solution changes from a Newtonian fluid to a non-Newtonian fluid.[130,131] In Nikerson and Paulson's study, the critical overlap concentration for sodium alginate solution was determined as the inflection point in a log-log plot of specific viscosity [$\eta_{sp} = (\eta_{solution} / \eta_{solvent}) - 1$] as a function of concentration with a value of ~0.35% w/w. However, the experimental method used in the Nikerson and Paulson[40] study may not be sensitive enough to detect the critical overlapping concentrations. A previous study showed that sodium alginate solutions with concentration of 0.1% w/v already exhibit shear-thinning behavior.[128] It is possible that sodium alginate chains may start to overlap each other at concentrations at a much lower concentration than 0.1% where the change in specific viscosity is not large enough to be detected experimentally.

Rezende *et al.*[37] performed both steady shear and small amplitude oscillation studies on sodium alginate (one unspecified grade purchased from Panreac, Barcelona, Spain) solutions at 2%, 3%, and 5% w/v for the determination of optimal design parameters for an alginate-based biomanufacturing system (alginate scaffold). Their findings showed that alginate solutions in the concentration range investigated underwent shear-thinning effects with increasing shear rates. It was also observed that the loss modulus was higher than the storage modulus and both moduli were dependent upon the frequency, which was a typical characteristic of dilute polymer solutions. Sodium

alginate solution at 5% w/v studied by Rezende *et al.*[37] is the highest sodium alginate solution studied so far. Even at 5% w/v, sodium alginate solution still shows more viscous behavior than elastic behavior.

Most of the sodium alginates employed in the previous studies were not pharmaceutical grades. For that matter, explicit recommendations have not been made in the literature as to the rheological methods that would be most appropriate for polymeric excipient evaluation relative to pharmaceutical processing or formulation performance. In addition, the previous studies were limited to the rheological characterization of sodium alginate solutions with concentrations lower than 5% w/v. Sodium alginate solutions with concentrations higher than 5% w/v or w/w would be expected to exhibit more elastic behavior and would provide valuable information on how sodium alginate behaves in formulations such as matrices during swelling and erosion.

As demonstrated in the preceding literature review, excipients, especially polymeric excipients, could be a major source of variability in pharmaceutical products. There is a need to further understand the inter-grade and inter-batch variability of polymeric excipients and the effect of their variability on their performance in different formulations. Sodium alginate is selected in these studies. Rheological methods could be an effective method of characterizing sodium alginate with the potential of revealing its physicochemical properties and its behavior in processing and final performance in formulations. Further studies on rheological properties of sodium alginate are necessary to prove the usefulness of this analytical method in the identification of the inter-grade and inter-batch variability of sodium alginate.

CHAPTER 2. RHEOLOGICAL EVALATION OF INTER-GRADE AND INTER-BATCH VARIABILITY OF SODIUM ALGINATE

Introduction

According to Quality-by-design (QbD) principles,[1] a design space for each pharmaceutical product could be established by encompassing, in part, the active pharmaceutical ingredient(s), the unit operations employed to produce the finished product, and the excipients.[2] Polymeric excipients, in particular, comprise mixtures of

polymers of different molecular weights and chemical composition and tend to be the least well-characterized components of the pharmaceutical products. This work focuses on the widely used, but poorly characterized polymeric excipient, sodium alginate, which is extracted from seaweeds.

Sodium alginates are linear, unbranched, amorphous copolymers of β-D-mannuronic acid (*M*) and α-L-guluronic acid (*G*) linked to each other by 1→4 glycosidic bonds. The *M* and *G* units in the alginates may be randomly or non-randomly arrayed as heterogeneous or homogeneous sequences. Due to the differences in steric hinge between adjacent monomers with respect to glycosidic bond rotation, the stiffness of the sequences in aqueous solution increases in the order $MG < M < G$. [58-60]

Due to their abundance, low price, and compatibility with biological systems, sodium alginates are widely used in the pharmaceutical and biomedical areas.[29] Pharmaceutically, sodium alginates are generally used as binding agents in tablets, as suspending and thickening agents in suspensions, water-miscible gels, lotions and creams, as emulsion stabilizers, or as gel-forming agents in combination with divalent metal ions such as calcium.[30] Since sodium alginate can almost immediately form a viscous layer when in contact water, it is employed in the development of alginate-based controlled release drug delivery systems, such as matrix tablets, microcapsules, etc.[29]

More than 200 different alginate grades — varying in molecular weight and chemical composition — are available from various manufacturers.[29] The heterogeneity of commercial pharmaceutical-grade alginates reflects differences among the botanical sources, seaweed harvesting locations, the season of harvesting, the plant parts employed, and the processing methods used.[54] Current pharmacopoeial specifications (USP -NF) for

sodium alginate do not enable the characterization of variations in the molecular weight distribution and/or chemical composition of sodium alginate. Since these variations can markedly affect the processability or performance of a sodium alginate-containing pharmaceutical product,[31,32] adherence to the USP-NF monograph may not ensure the interchangeability of sodium alginates from different sources or even various batches from the same manufacturer. Previous studies have shown that the inter-manufacturer and/or inter-batch (lot) variability of excipients can exert a significant effect on the performance of the final formulations, even though these excipients meet the pharmacopoeial specifications.[10,11,15,16,21] It is not surprising that pharmacopoeial specifications are not guarantors of excipient performance, because they focus on identity, purity, and safety. Thus, it is important for pharmaceutical manufacturers to develop effective methods for the characterization of sodium alginate in order to help establish the design space for sodium alginate-based formulations.[1]

An effective method of excipient characterization should reflect the excipient's behavior during processing and its functionality in potential formulations. Sodium alginates are mostly used as binders, thickeners and gel-forming agents in both conventional and controlled release formulations. The functionality of sodium alginate in these formulations can be related to its rheological behavior in aqueous solutions. Steady shear rheological methods are eminently suitable for determination of solution flow behavior, which is critical for certain types of formulations, *e.g.*, suspensions and emulsions. However, under steady shear, the underlying structure of the polymer network in solutions is destroyed. Solutions with high polymer concentrations, such as those present in the gel layer around an alginate-based matrix, are better characterized by

methods such as small amplitude oscillation (SAO) tests that are less likely than steady shear methods to disturb or disrupt the polymer network. Therefore, both steady shear and SAO rheological methods should be useful in characterization of sodium alginate. Unfortunately, the rheological properties of sodium alginate solutions are not specified in the United States Pharmacopoeia (USP33-NF28, 2010).

Even though a proposed chapter for the USP-NF on excipient performance[51] suggests that viscosity tests be employed to assess the functionality of excipients used as thickening agents, the current pharmacopoeial chapter on viscosity testing does not mandate test conditions that reflect actual usage of the excipients. Even when excipient manufacturers do supply rheological data for sodium alginates, they typically only report the apparent viscosities of sodium alginate solutions at one specific concentration, at one shear rate, and at one temperature — "one-point" measurements — as if the alginate solutions' rheological characteristics were those of Newtonian fluids. In fact, the typical rheological behavior of many polymer solutions is highly shear- and concentration-dependent, encompassing the range from Newtonian to shear-thinning non-Newtonian to viscoelastic behavior.[33,34] The shear rates encountered in pharmaceutical manufacturing and in product use can vary considerably, ranging from 10^{-3} to 10^{6} s^{-1}.[35] Thus, "one-point" apparent viscosity values provide little to no insight into the selection of suitable polymer grades for a specific formulation or manufacturing process.[36] A comprehensive rheological evaluation of sodium alginate solutions is warranted in order to facilitate the identification of criteria that would allow inter-grade or inter-batch comparisons.

Although a number of studies have been published on the rheological behavior of sodium alginate solutions,[37-47] most of the sodium alginates employed in these studies

were not pharmaceutical grade. In addition, these studies were limited to the rheological characterization of sodium alginate solutions at concentrations lower than 5% w/v. Sodium alginate solutions at these low concentrations exhibit fluid-like behavior, whereas sodium alginate solutions at higher concentrations display a more substantial viscoelastic character. Unfortunately, no studies have been conducted on these more highly concentrated, substantially viscoelastic solutions of sodium alginate.

QbD necessitates an understanding of the rheological behavior of the excipient utilizing experimental conditions and excipient concentrations appropriate to the formulation and processes under consideration. The absence of meaningful, published data underscores the need for rheological methods that would be appropriate for polymeric excipient evaluation relative to pharmaceutical processing and formulation performance. Since rheological measurements generate numerical test results instead of limit test results, summary statistics of the grade-to-grade and batch-to-batch rheological parameters will benefit both the excipient manufacturer and pharmaceutical manufacturer.

A persistent problem in traditional formulation development stems from the lack of awareness or ignorance of excipient variability. Following QbD principles, users need to understand the inter-grade and inter-batch variability of excipients and its possible impact on formulation processing and product performance. This work is intended to determine the inter-grade and inter-batch variability of sodium alginate using appropriate rheological methods and conditions, thereby providing insight into the delineation of the design space as part of QbD for sodium alginate-based formulations.

Materials and Methods

Materials

Six grades of sodium alginate (comprising one batch of each grade) — produced by FMC Biopolymer (Drammen, Norway) — representing a wide range of reported viscosities, were provided by the manufacturer (Table 4), along with 10 additional batches of one of the grades (LF120M, Table 5: batches were designated from *A* to *J* based on manufacturing date). Deionized water was obtained from a Milli-Q ultrapure water system (Millipore Corp., Billerica, MA, USA). Sodium chloride (ACS grade) was purchased from Sigma Aldrich (St. Louis, MO, USA) and used as supplied.

Table 4. Sodium alginate grades and physicochemical properties specified by FMC Biopolymer.

Grade	FMC Product Name	%G	Viscosity range[a], mPa•s
1	**Protanal LF10/60LS**	35-45	20-70
2	**Protanal LF240D**	30-35	70-150
3	**Protanal LF120M**	35-45	70-150

4	**Protanal LF200M**	35-45	200-400
5	**Protanal LF200DL**	55-65	200-400
6	**Protanal HF120RBS**	45-55	600-800

[a]: Viscosity data reported in manufacturer's certificate of analysis [Viscosity was determined for 1% w/v sodium alginate solutions at 20 ºC using a Brookfield viscometer, spindle #3 at 40 rpm].

Table 5. Ten batches of sodium alginate — Protanal LF120M — produced in 2007 and physicochemical properties specified by FMC Biopolymer.

Batch	**Manufacturer's Batch #**	**Manufacturing Date**	**Viscosity[a], mPa•s**
A	19338	**01-23-2007**	95
B	19440	**02-26-2007**	97
C	19626	**04-24-2007**	109

D	19664	**05-11-2007**	104
E	19748	**06-04-2007**	97
F	19812	**06-15-2007**	99
G	19961	**08-20-2007**	96
H	20041	**09-11-2007**	101
I	20076	**10-10-2007**	112
J	20228	**11-12-2007**	105

[a]: Viscosity data reported in manufacturer's certificate of analysis [Viscosity was determined for 1% w/v sodium alginate solutions at 20 ºC using a Brookfield viscometer].

Methods

Calcium Content Determination

Aqueous sodium alginate solutions (0.1% w/v) were prepared and the calcium content then determined by fitting the atomic absorption of sodium alginate solution at 423 nm obtained on Atomic Absorption Spectrophotometer (Model 1100, Perkin-Elmer, MA, USA) to a standard curve.[132]

Determination of % G by Solid-State ^{13}C NMR (SSNMR) (Work done in Dr. Eric J. Munson's lab at the University of Kansas)

The %G in the intact sodium alginate powders were determined by SSNMR: Solid-state ^{13}C NMR spectra were acquired using a Chemagnetics CMX-300 spectrometer (Varian, Inc., Fort Collins, CO, USA) operating at approximately 75 MHz for ^{13}C. Chemagnetics double-resonance probes equipped with Revpljk.olution NMR 7-mm spinning modules (Revolution NMR, LLC, Fort Collins, CO, USA) were used to acquire all spectra. Samples were packed into zirconia rotors and sealed with Teflon end-caps. Spectra were acquired using ramped-amplitude cross-polarization, magic-angle spinning (MAS) with total sideband suppression, and SPINAL64 decoupling. Spectrometer settings were optimized and the reference frequency set using 3-methylglutaric acid. A contact time of 1 ms, MAS frequency of 4.0 kHz, and a ^{1}H-decoupling field of approximately 80 kHz were used to acquire all spectra. The recycle delays varied based upon ^{1}H T_1 values for each sample, which were measured using saturation recovery experiments. Using Chemagnetics Spinsight software plots of integrated signal intensity versus saturation recovery times were fit to Eq. 16:

$$y = amp(1 - e^{\tau/T_1}), \qquad \text{Equation 16}$$

where y is the integrated signal intensity, amp is the amplitude constant, τ is the saturation recovery time, and T_1 is the spin-lattice relaxation time. Saturation recovery times were arrayed from 0.01 to 10 s, and monoexponential curve-fitting provided an accurate fit for all data sets. A recycle delay equal to 5 times the ^{1}H T_1 value of each sample was used to acquire each spectrum. A total of 5120 transients were acquired in order to achieve a high signal-to-noise ratio (SNR). Deconvolution of peaks in the region 60-90 ppm was achieved using Chemagnetics Spinsight software, and peak areas were

then used to calculate the amount of guluronic and mannuronic acid present in each sample.

Intrinsic Viscosity

The apparent viscosities of aqueous sodium alginate solutions containing sodium chloride (0.1 M) and of the solvent, $\eta_{solution}$ and $\eta_{solvent}$, respectively, were evaluated at 25°C by using an Ubbelohde viscometer (Cannon Instruments, State College, PA, USA). All alginate concentrations reported in this work were corrected for moisture content. Moisture content was determined as the weight loss of sodium alginate samples kept at 105°C for 4 hours using Thermogravimetric Analysis (TA Instruments, New Castle, DE, USA). Intrinsic viscosities [η] were determined from the concentration dependence of the reduced specific viscosity $\frac{\eta_{sp}}{C}$ in accordance with the Huggins equation:

$$\frac{\eta_{sp}}{C} = [\eta] + k' \cdot [\eta]^2 \cdot C \ , \qquad \text{Equation 17}$$

where C is concentration, g/dL, k' is a constant, and η_{sp} is specific viscosity:

$$\eta_{sp} = \frac{\eta_{solution}}{\eta_{solvent}} - 1 \qquad \text{Equation 18}$$

Intrinsic viscosity is the hydrodynamic volume of polymer chains at infinitely diluted concentration with a unit of dL/g. Weight average molecular weight (M_w) and number average molecular weight (M_n) were calculated according to Mark-Houwink-Sakura equation with the following constants:[133]

$$[\eta] = 0.023 \bullet M_w^{0.984} \Rightarrow M_w = \left(\frac{[\eta]}{0.023} \right)^{\frac{1}{0.984}} \qquad \text{Equation 19}$$

$$[\eta] = 0.095 \bullet M_n^{0.963} \Rightarrow M_n = \left(\frac{[\eta]}{0.095} \right)^{\frac{1}{0.963}}$$ Equation 20

where M_w and M_n are expressed in *kDa*. The constants were obtained by fitting intrinsic viscosity data of sodium alginates to average molecular weight obtained from gel permeation chromatograph and laser scattering characterization.[133]

Steady Shear

Since sodium alginate is commonly used as a thickening agent in suspensions or emulsions at concentrations ranging from 1 to 3%,[30] steady shear measurements were performed on sodium alginate solutions at 1%, 2%, and 3% w/w for the six grades, and 2% w/w for the 10 batches of grade 3 using a controlled stress/rate (CS/CR) rheometer (AR-2000, TA Instruments, New Castle, DE, USA) with a steel cone-and-plate accessory (ϕ = 40 mm; θ=1°). Sample temperatures were maintained at 25 ± 0.1°C by a Peltier temperature-control system. The rotational rheometer was validated with Cannon viscosity standard N35 (Cannon Instruments, State College, PA, USA) (Appendix I).

Small Amplitude Oscillation (SAO)

SAO measurements were performed on sodium alginate solutions over a wide range of concentrations (4-13% w/w) using an AR-2000 CS/CR rheometer (TA Instruments, New Castle, DE, USA), equipped with a steel cone-and-plate accessory (ϕ = 40 mm; θ = 1°). Frequency sweeps were performed with the angular frequencies (ω) ranging from 1 to 100 rad/s at 25°C and/or 37ºC with 10% strain. Strain sweeps from 1 to 100% were carried out to make sure that the 10% strain applied during the frequency

sweep was in the linear viscoelastic region for the samples tested. Sample temperatures were maintained at 25 ± 0.1°C or 37 ± 0.1°C by a Peltier temperature-control system. The rheometer was validated by performing frequency sweep measurements on a standard material ─ liquid isoprene rubber (LIR50), a linear monodisperse 1,4-polyisoprene with a molecular weight of 45 kDa and polydispersity less than 1.1 (Kuraray American, Inc., Houston, TX, USA) (Appendix I).

Temperature Influence on Rheological Behavior

Steady shear and SAO studies were performed on solutions of one selected grade (grade 3: LF120M) of sodium alginate at various concentrations (2, 3, 4, 5, and 8% w/w) and at two different temperatures (20ºC and 37ºC) in accordance with the above procedures. Temperature effects on the apparent viscosities of the 2% w/w aqueous solutions of the six grades of sodium alginate were further investigated at 15, 20, 25, 37, and 45 ºC.

Data Analysis

Rheological data of the solutions of sodium alginate were analyzed *via* analysis of variance (ANOVA) and Levene's test for homogeneity of variance using PASW Statistics 18 for Windows (SPSS Inc., Chicago, IL, USA). *Post hoc* testing ($p < 0.05$) of the multiple comparisons was performed by either the Tukey HSD (Honestly Significant Difference) test or Games–Howell test, depending on whether the outcome of Levene's test was insignificant or significant, respectively. Where appropriate, the following specialized software applications were also employed in the analysis of data: GraphPad

Prism (version 5, GraphPad Software, Inc., La Jolla, CA, USA), TableCurve 2D (version 5.01, Systat Software, Inc., San Jose, CA, USA), and TableCurve 3D (version 4.0, Systat Software, Inc., San Jose, CA, USA).

Results and Discussion

Inter-Grade Variability

Calcium Content, Chemical Composition, and Intrinsic Viscosities

Sodium alginate solutions' specific viscosities relative to concentration are plotted with respect to concentration in Figure 11. The intrinsic viscosities of the six grades of sodium alginate are corresponding to the y-axis intercepts of the linear regression of their respective data sets.

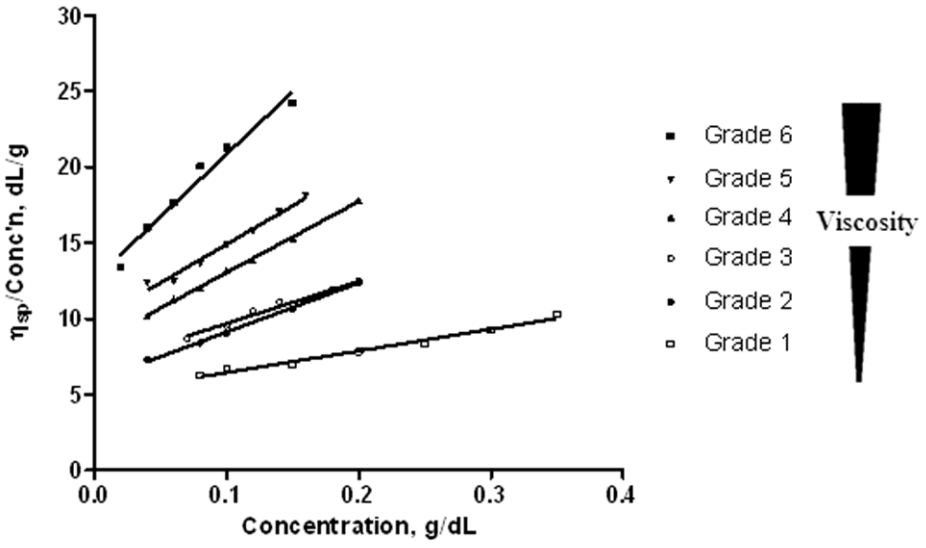


Figure 11. Sodium alginate solutions' specific viscosity/concentration with respect to concentration for the determination of intrinsic viscosity (0.1 M NaCl solution at 25°C). Data are shown as mean and standard deviation of three replicates.

The residual calcium content, chemical composition and intrinsic viscosity ($[\eta]$) data for the six grades of sodium alginate are listed in Table 6. Sodium alginate, extracted from seaweed using the calcium alginate method,[54] may have residual calcium that could influence the rheological properties of the resultant sodium alginate solution. In some instances, calcium salts are added to sodium alginate to increase viscosity of the corresponding polymer solutions.[54] The residual calcium content of the sodium alginate powder employed in this study was found to vary from 0.08% to 0.51% w/w. The corresponding molar ratios of calcium to sodium alginate monomer range from 0.004 to 0.025. Since calcium:alginate monomer molar ratios below 0.05 have been reported to exert little or no effect on the apparent viscosities of aqueous alginate solutions (measured at two different rates of shear),[134] the ratios determined for these sodium alginates used in this study do not warrant concerns regarding the possible untoward influence of calcium on solution rheology.

Table 6. Calcium content, %G, $[\eta]$, and average molecular weights calculated based on the intrinsic viscosities of the six grades of sodium alginate. Mean and standard deviation were calculated from three replicates.

Grade	Calcium (%) (Mean ± S.D.)	%G per FMC (% Range)	%G per SSNMR (% Range)	[η] (dL/g) (Mean ± S.D.)	*Average* M_w (kDa)	*Average* M_n (kDa)
1	0.42 ± 0.0023	35-45	37 - 42	5.53 ± 0.15	263	68
2	0.51 ± 0.0023	30-35	33 - 36	6.04 ± 0.09	288	75
3	0.41 ± 0.0039	35-45	38 - 42	6.43 ± 0.06	306	80
4	0.26 ± 0.0023	35-45	39 - 43	8.72 ± 0.24	418	109
5	0.08 ± 0.0039	55-65	48 - 53	8.54 ± 0.12	409	107
6	0.28 ± 0.0023	45-55	43 - 47	11.26 ± 1.21	541	142

The guluronic acid percentages (%G) of the different grades — as determined in our study — are within the ranges specified by the manufacturer, except for grades 5 and 6 for which the %G values determined by solid-state NMR (SSNMR) are slightly lower than the values listed in the manufacturer's specifications. The range of %G reported by the manufacturer was determined using ^{1}H NMR spectroscopy in solution. As sample preparation for solution NMR requires partial acid hydrolysis of the alginate chain, sample alteration or loss of insoluble material can occur.[135,136] Therefore, analysis of the intact solid sample may actually give a better representation of the alginate composition.

The range of intrinsic viscosities (and the corresponding molecular weights) of the sodium alginate differs by approximately two-fold among the six grades. The rank order of intrinsic viscosities of the six grades corresponds, approximately, to the viscosity range specified by the manufacturer: the higher the viscosity grade, the higher the

intrinsic viscosity. Interestingly, although there are differences in the intrinsic viscosities of grades 2 and 3, these two grades are characterized by the manufacturer as having the same range of solution viscosities. This is also true for grades 4 and 5. The viscosity range provided by the manufacturer for each grade is in fact very wide. It is not surprising that grades with the same viscosity specification could still vary substantially in their average molecule weight.

Steady Shear

The steady shear rheological properties of the solutions of the six grades of sodium alginate at 1, 2, and 3% w/w concentrations, at 25°C, are depicted in Figure 12, where the apparent viscosity (η_{app}) or shear rate is plotted as a function of shear stress.

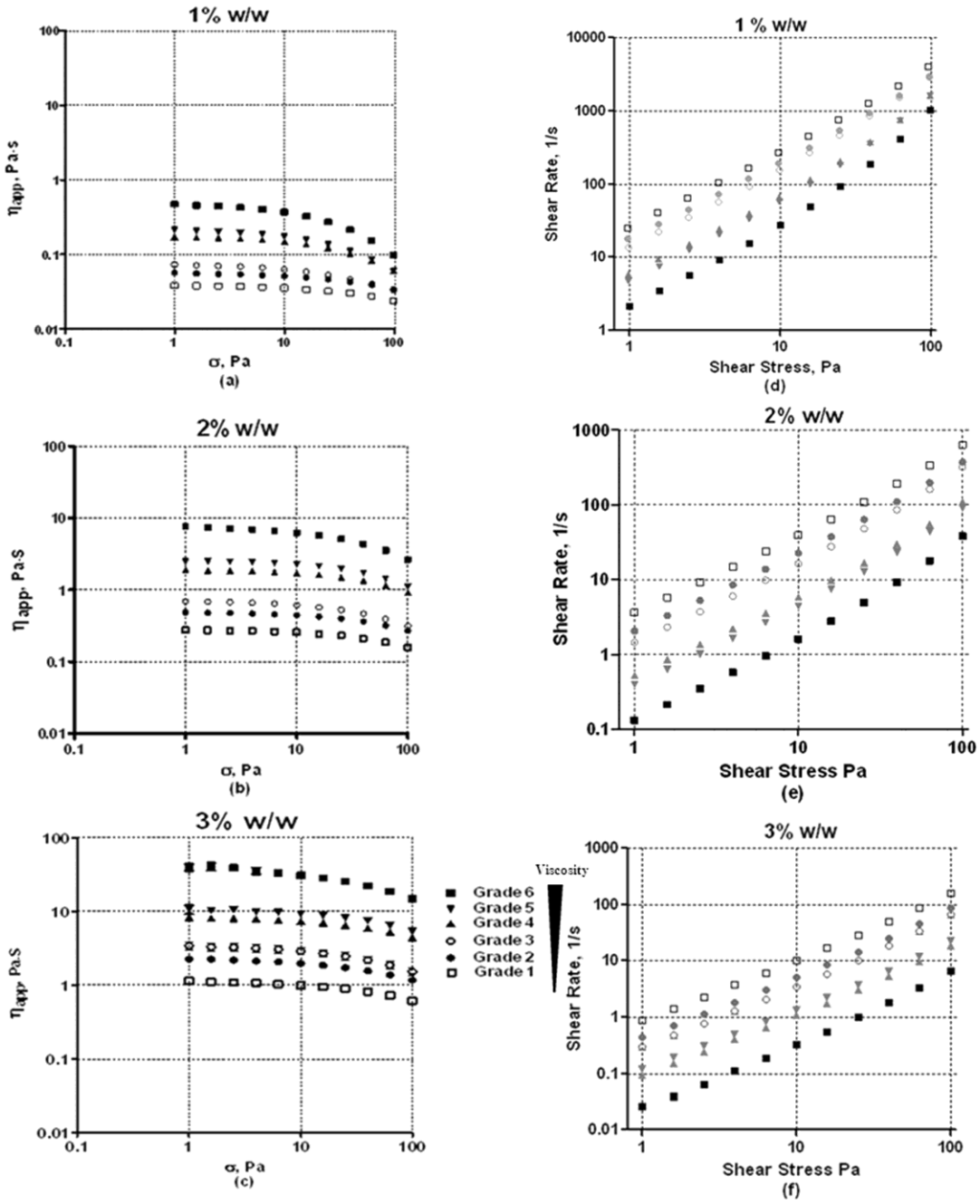


Figure 12. Steady shear results of sodium alginate solutions at three concentrations at 25°C: apparent viscosity as a function of shear stress for (a) 1%; (b) 2%; and (c) 3% w/w solutions; shear rate as a function of shear stress for (d) 1%; (e) 2%; and (f) 3% w/w solutions. Data are shown as mean and standard deviation of six replicates.

The apparent viscosities of all the alginate solutions decrease with increasing shear stress. Shear rate and shear stress data were fitted by the following power-law model (Equation 3 in Chapter 1):

$$\dot{\gamma} = k \cdot \sigma^{n}, \qquad \text{Equation 3}$$

where $\dot{\gamma}$ is shear rate (1/s), σ is shear stress (Pa), k is a constant, and n is the power law index. For shear-thinning fluids, $n > 1$. The larger the value of the power-law index, the more shear-thinning the solution. The n values for the solutions of six grades of sodium alginate at three concentrations are summarized in Table 7. Based on n values, all six grades of sodium alginate are showing shear-thinning behavior in the concentration ranges investigated. It is consistent with previous observations of shear-thinning behavior of solutions of sodium alginate at these concentrations.[37,39,47,133] Generally, those grades with lower apparent viscosities also show a smaller n values, which indicates that grades with lower viscosity are less shear-thinning than grades with higher apparent viscosities. For those grades with relatively lower apparent viscosities (Grades 1, 2, and 3), their n values keep almost constant from 1% to 3% w/w. For those grades with relatively higher apparent viscosities (Grades 4, 5, and 6), their n values decrease from 1% to 3% w/w. With a higher number of polymer chains in solutions at higher concentrations, larger shear stress is required to align the polymer chains along the flow direction. The dragging effects of sodium alginate molecules in solution are more obvious for those grades with larger molecular weights (long polymer chains in solution) than those grades with smaller molecular weights.

Table 7. Power-law index values for sodium alginate solutions (six replicates).

Sodium Alginate	n		
	1% w/w	2% w/w	3% w/w
Grade 1	1.244 ± 0.011	1.293 ± 0.020	1.274 ± 0.016
Grade 2	1.244 ± 0.018	1.295 ± 0.020	1.294 ± 0.016
Grade 3	1.355 ± 0.018	1.401 ± 0.013	1.374 ± 0.040
Grade 4	1.562 ± 0.036	1.392 ± 0.021	1.292 ± 0.015
Grade 5	1.679 ± 0.039	1.458 ± 0.017	1.327 ± 0.011
Grade 6	1.873 ± 0.047	1.529 ± 0.025	1.411 ± 0.011

The rank-order of the various sodium alginate grades based on the apparent viscosities of their solutions is *grade 1* < *grade 2* < *grade 3* < *grade 4* < *grade 5* < *grade 6* for all three concentrations at low shear stress (1-25 Pa). Statistical analysis (ANOVA) of the steady shear data (six replicates) shows that apparent viscosities of the six grades are significantly different from each other at all three concentrations ($P < 0.001$) at low shear stress (1-25 Pa). *Post hoc* multiple comparisons reveal that all these grades are significantly different from each other at each concentration. It is also evident from Figure 12 that the differences in apparent viscosity among these grades of sodium alginate become larger at higher alginate concentrations or at lower shear stresses. The "one-point" viscosity data reported by the manufacturer were measured using Brookfield viscometer (Middleboro, Massachusetts, USA) at 40 rpm, which corresponds to 0.25 to 2.5 Pa shear stress based on the conversion method developed by Rosen *et al.*[137] The viscosity ranges provided by the manufacturer for specific grades of sodium alginate are relatively large and overlapping. For example, the manufacturer's brochure shows the

same viscosity range for grades 4 and 5 (200-400 mPa•s) and for grades 2 and 3 (70-150 mPa•s). Obviously, this viscosity data does not reflect the variation in apparent viscosity of sodium alginate solutions at different concentrations under different conditions. Thus, those alginate grades specified by the manufacturer as having the same viscosity range may show significant differences in their rheological behavior under different conditions corresponding to a specific process or product use. It is important to determine the apparent viscosities at concentrations and shear conditions relevant to the formulations, *e.g.*, apparent viscosities at low shear (*e.g.*, 1 – 50 s^{-1}) can be useful in the development of a suspension formulation, while apparent viscosities at high shear (> 10,000 s^{-1}) [35,123] are more appropriate for solutions used in coating or spray-drying processes.

As to the effect of polymer concentration on the apparent viscosities of these solutions at low shear stress, *e.g.*, 1 Pa, the range of the apparent viscosities of the six grades of sodium alginate in solution is ~10-fold at 1% w/w, ~28-fold at 2% w/w, and ~33-fold at 3% w/w. At high shear stress, *e.g.*, 100 Pa, the range of the apparent viscosities of the six grades of sodium alginate in solution is ~5-fold at 1% w/w, ~16-fold at 2% w/w, and ~24-fold at 3% w/w. Apparently, the difference in average molecular weight among the various grades of sodium alginate are associated with disproportionately greater differences in apparent viscosities, especially at lower shear stresses and higher concentrations. Furthermore, the apparent viscosities increase > 6-fold for each grade from 1% to 2% and > 4-fold from 2% to 3%. This disproportionate increase in apparent viscosity is the result of the disproportionate increase in likelihood of polymer chain interactions in solution. In addition, grades with higher M_w show a larger-fold increase in their apparent viscosity at higher concentrations, *e.g.,* from 1% to 2%

w/w, apparent viscosity of grade 1 solution increases ~6 times while that of grade 6 solution increases ~15 times. This observation is in accordance with the previously reported empirical relationship[138-140] between polymer solution viscosity, concentration, and molecular weight:

$$\eta_{solution} = \eta_{solvent} \cdot \exp(aC^x M^y), \qquad \text{Equation 21}$$

where M is polymer weight-average molecular weight, C is polymer concentration, $\eta_{solution}$ and $\eta_{solvent}$ are polymer solution and solvent apparent viscosity at a specified shear stress/rate, respectively, and a, x, and y are constants. Thus, higher polymer concentrations or larger polymer molecular weights M_w are associated with higher solution viscosities. Those polymers with higher M_w would show a larger-fold increase in viscosity with increasing concentration. Fitting our data to this equation results in Figure 13, where apparent viscosities (1 Pa shear stress, 25°C) of sodium alginate solutions are plotted as a function of alginate concentration and the M_w values estimated from the corresponding intrinsic viscosities (r^2=0.966, a=0.085, x=0.426, y=0.694). However, there are only six different grades available for model fitting, the validity of the model will need to be tested with additional data.

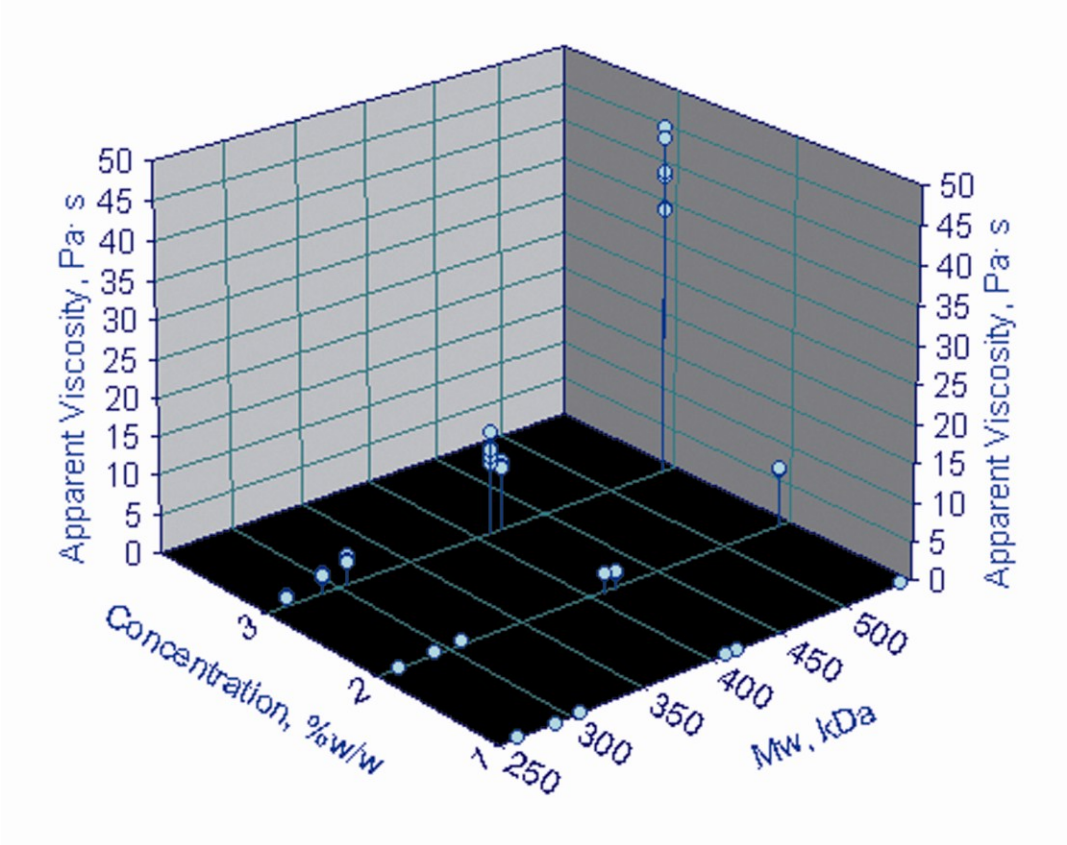


Figure 13. The relationship among apparent viscosities (1 Pa shear stress, 25°C) of sodium alginate solutions, sodium alginate concentration, and molecular weight.

The apparent viscosities of solutions of these six grades are consistent, for the most part, with the expectation that higher average molecular weights would result in higher apparent viscosities. This is depicted in Figure 14 where apparent viscosities (1 Pa shear stress, 25°C) of sodium alginate solutions are plotted as a function of the M_w values estimated from the corresponding intrinsic viscosities. Since sodium alginate is a linear unbranched polymer, higher molecular weights increase the likelihood of inter-chain interactions in solution resulting in correspondingly higher viscosities.

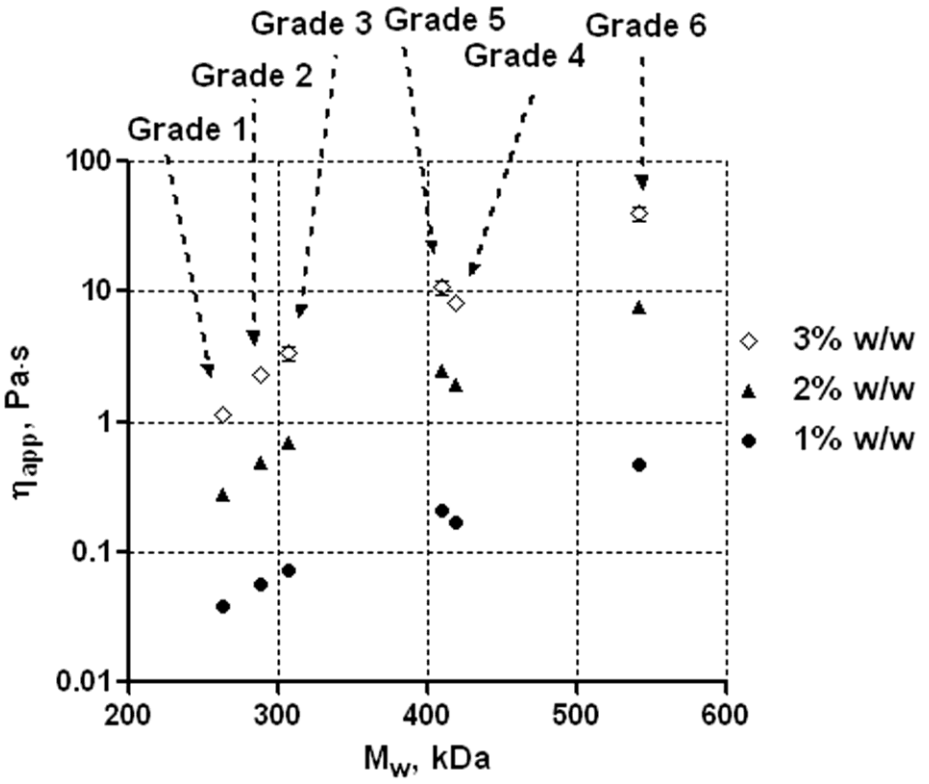


Figure 14. Apparent viscosities (shear stress = 1 Pa; 25°C) of sodium alginate solutions (1%, 2%, and 3% w/w) as a function of average M_w (calculated based on intrinsic viscosities). Data are shown as mean and standard deviation of six replicates.

One anomaly in the data is that grade 5 results in apparent viscosities that are significantly higher than those for grade 4 at corresponding shear stresses. On one hand, grade 5 has an average molecular weight that is slightly less than that of grade 4. On the other hand, grade 5 is higher in %G than grade 4. Thus, a possible explanation for this anomalous rheological behavior is that the higher %G in the alginate molecular chain of grade 5 leads to stiffer, *i.e.*, more extended, chain conformations in solution [58-60] and an increased likelihood of inter-chain interaction under steady shear.

The contribution of average molecular weight and %G to apparent viscosity of alginate solutions is typified by the graph in Figure 15, where the apparent viscosity of 2% w/w solutions (1 Pa shear stress, 25°C) is shown as a function of both M_w and %G. The empirical relationship among the variables may be expressed in terms of the least squares-fitted equation (per TableCurve 3D) as follows:

$$\ln(\eta_{app}) = 3.85 + 5.81\times10^{-6} \bullet (\%G)^3 + 9.98\times10^{-3} \bullet M_w, \qquad \text{Equation 22}$$

where r^2 is 0.998. This empirical equation needs to be validated with additional data obtained from different grades with varying %G and molecular weight.

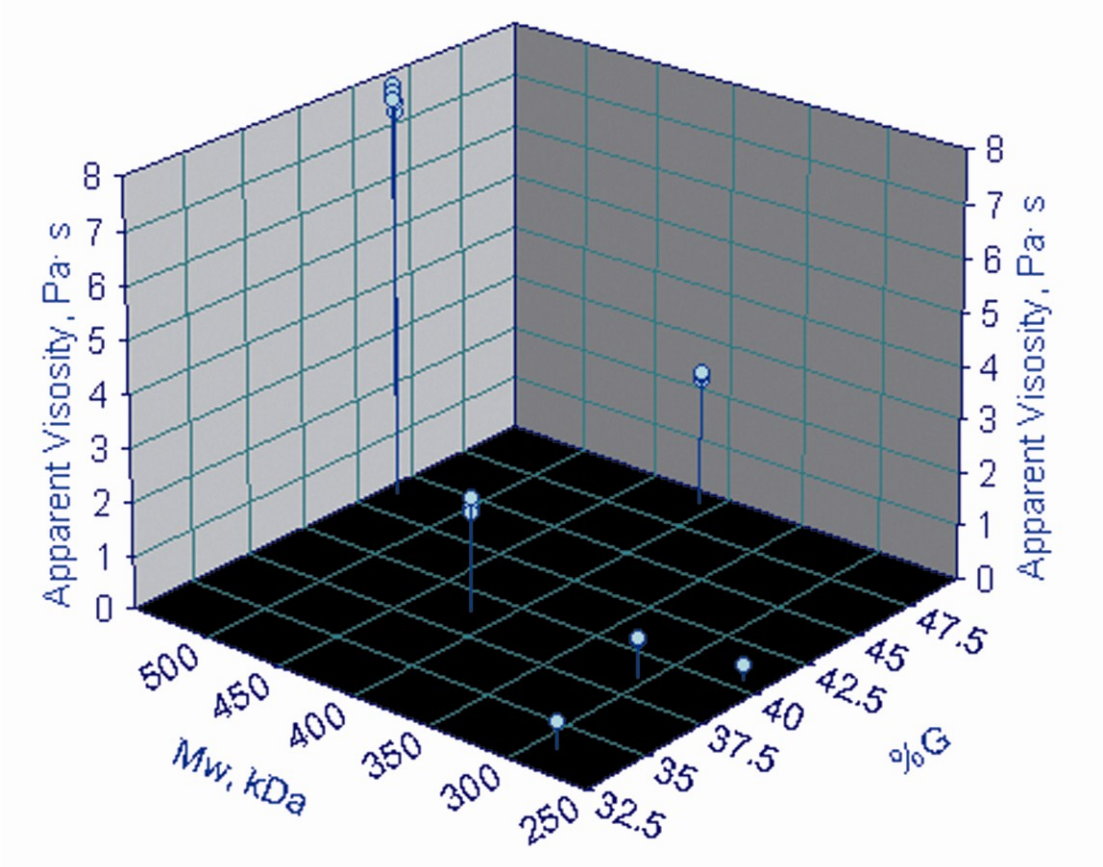


Figure 15. The relationship among apparent viscosity (1 Pa shear stress, 25°C) of 2% w/w sodium alginate solutions, M_w, and %G.

Although size exclusion chromatography has been used to determine the molecular weight distribution of polymeric excipients and NMR has been employed to characterize the chemical composition of such excipients, rheological methods are easier to perform and can measure functionality-related properties of the excipients in a relatively short time period. Furthermore, rheological behavior is indicative of the molecular weight distribution of a polymeric mixture.[112-114] Thus, steady shear behavior under specific shear conditions can be employed for assessment of the quality of polymeric excipients used as thickening or binding agents prior to product manufacturing. This work focuses on different grades of excipient from the same manufacturer, but the same methods can be applied to ensure interchangeability or equivalence of an excipient from different manufacturers.

A specific range of apparent viscosities can be achieved by employing different grades of sodium alginate at different concentrations. Therefore, for those formulations whose functionality can be related to apparent viscosity, multiple grades of sodium alginate could be included as long as alginate concentration and mechanical conditions (*e.g.*, shear rate or stress) were also specified. For example, when developing a suspension with desired apparent viscosities between 150 mPa·s and 300 mPa·s under low shear conditions (*i.e.*, 1-10 Pa), grades 2 or 3 at 1% w/w, or grade 1 at 2% w/w, would be recommended. It is more reasonable and practical to employ the apparent viscosity values as justification for inclusion of excipients in a formulation — by

adjusting excipient concentrations to achieve the same apparent viscosities— than by selecting excipients based on their apparent viscosity data at one concentration. The inclusion of multiple excipient grades in the formulation design would be especially important when excipient production or availability is problematic. In fact, the concept of formulation design space was proposed to FDA as a post-approval activity during FDA generic drugs workshop in June 2009.[141]

Small Amplitude Oscillation

Strain Sweep

Strain sweep experiments were conducted on sodium alginate solutions. The strain dependence of the storage modulus G', at a fixed angular frequency of 1.0 rad/s, is exemplified by the 8% w/w sodium alginate solutions as shown in Figure 16 (details for other concentrations are listed in Appendix I). For all six grades, the G' value remains approximately the same until strain exceeds 40% at which more than a 10% drop of G' is observed. The 10% strain used in frequency sweep in this work is, therefore, within the linear viscoelasticity range of alginate solutions. The applied strain in each frequency sweep measurement would not destroy or disrupt the polymer network/entanglements in the investigated sodium alginate solutions.

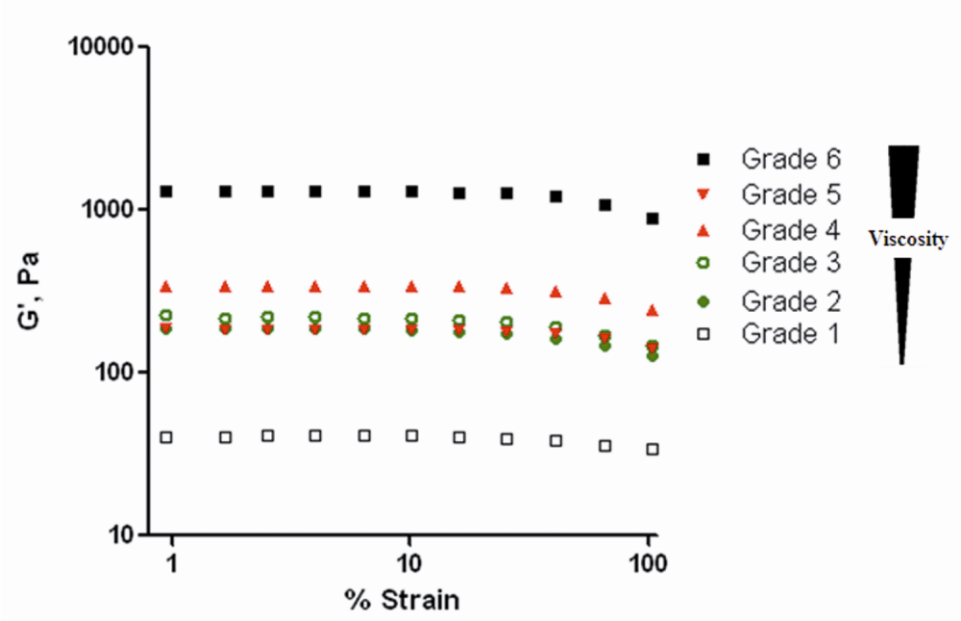


Figure 16. The storage modulus G' as a function of %strain for 8% w/w alginate solutions at 37°C.

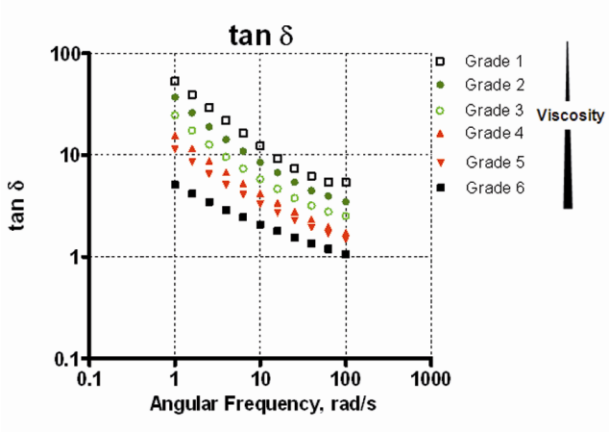
Viscoelasticity

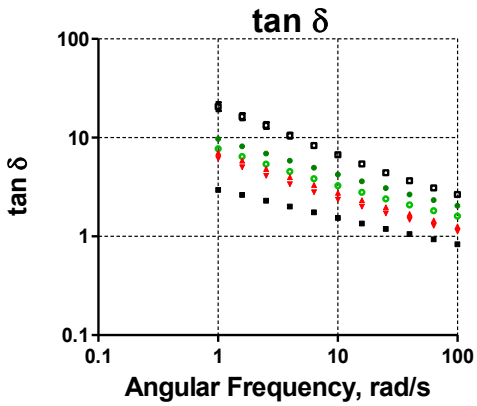
At 1% w/w concentration, sodium alginate solutions show little evidence of elastic behavior or network formation: the values of storage modulus G' are negligible. However, at concentrations ≥ 2% w/w, the viscoelastic moduli (storage modulus G', loss modulus G'') are more substantial. SAO results for 2% and 3% w/w solutions are shown in Figure 17 in terms of G', G'', and tan δ, *i.e.*, the ratio of the loss modulus (G'') to the storage modulus (G'). Higher alginate concentration leads to higher values of G′ and G'', and lower values of tan δ for all six grades of sodium alginate.

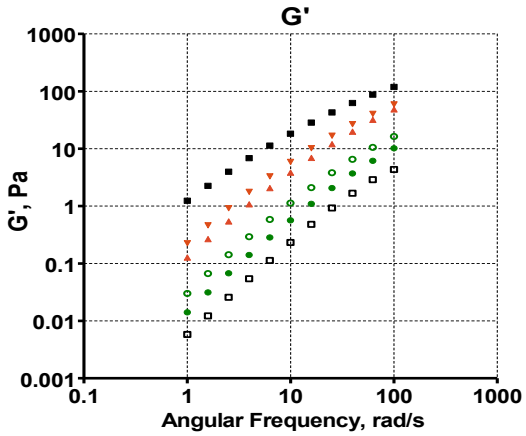
ANOVA tests of tan δ of solutions of these grades at both concentrations showed significant differences among these six grades of sodium alginate ($P < 0.001$). The results of *post hoc* multiple comparisons test indicate that grades 4 and 5 do not show any

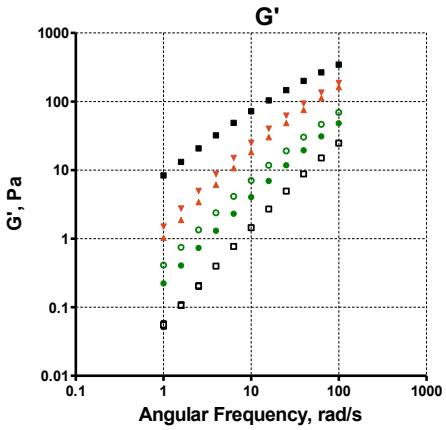
significant differences in their viscoelasticity at 2% and 3% w/w. Interestingly, there is no significant difference in tan δ between grades 3 and 4 at 3% w/w although their apparent viscosities are significantly different at this concentration. Thus, grades that are significantly different in their apparent viscosities may not necessarily be significantly different in their viscoelastic parameters at the same concentration.

Apparent viscosities are mainly determined by inter-polymer interactions under steady shear. Since sodium alginate is a polydisperse mixture of molecules with different molecular weights and chemical composition, those molecules with a more extended conformation in solution would have more chances of interacting with each other under shear. On the other hand, viscoelasticity is a reflection of the polymer interactions under minor deformation. At these low concentrations, polymer chains do not form a 3-D network. Viscoelasticity is probably determined by the quasi-overlapping of adjacent polymer chains (their hydrodynamic spheres overlap each other) at these concentrations. One can assume, for the six grades of sodium alginates investigated, their intra-polymer, inter-polymer, and polymer-solvent interactions under steady flow and small amplitude oscillation are likely to vary. Sodium alginates differ in apparent viscosity may not differ in viscoelasticity and *vice versa*. This result emphasizes the importance of characterizing the steady shear behavior as well as the viscoelastic properties of sodium alginate solutions in order to identify the inter-grade and inter-batch variability.


tan δ
tan δ
100
10
1
0.1
0.1
1
10
100
1000
Angular Frequency, rad/s
Grade 1
Grade 2
Grade 3
Grade 4
Grade 5
Grade 6
Viscosity


tan δ
tan δ
100
10
1
0.1
0.1
1
10
100
Angular Frequency, rad/s


G'
G', Pa
1000
100
10
1
0.1
0.01
0.001
0.1
1
10
100
1000
Angular Frequency, rad/s


G'
G', Pa
1000
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Angular Frequency, rad/s

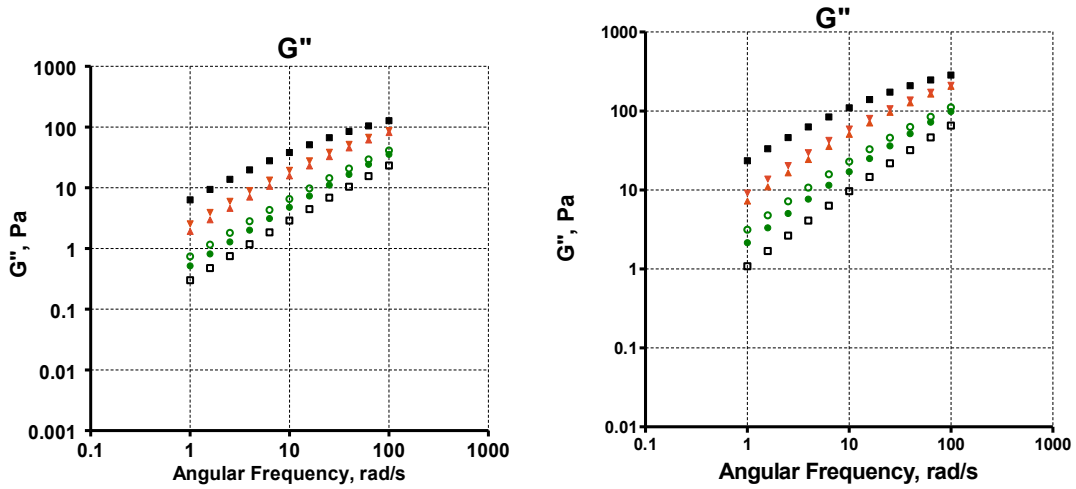

Figure 17. The tan δ , G', and G'' as a function of angular frequency (ω) for sodium alginate solutions at 2% (left) and 3% w/w (right) at 25°C. Data are shown as mean and standard deviation of six replicates.

Cox-Merz Rule

The quasi-empirical Cox-Merz rule states that the steady shear apparent viscosity (η_{app}) and the magnitude of the complex viscosity (η^*) of linear polymer solutions are superimposable at numerically equivalent values of shear rate (s^{-1}) and angular frequency (rad/s).[142,143] The complex viscosity is defined by

$$\eta^* = \frac{\left(G'^2 + G''^2\right)^{1/2}}{\omega}, \qquad \text{Equation 23}$$

As shown in Figure 18, rheological data for 2% w/w and 3% w/w solutions of the six grades of sodium alginate obey this rule. Conformity to the Cox-Merz rule is evidence for the absence of gel structure in these solutions.[144] It also confirms that the calcium content of these sodium alginates does not exert a significant effect on the rheological behavior of their solutions at these concentrations.

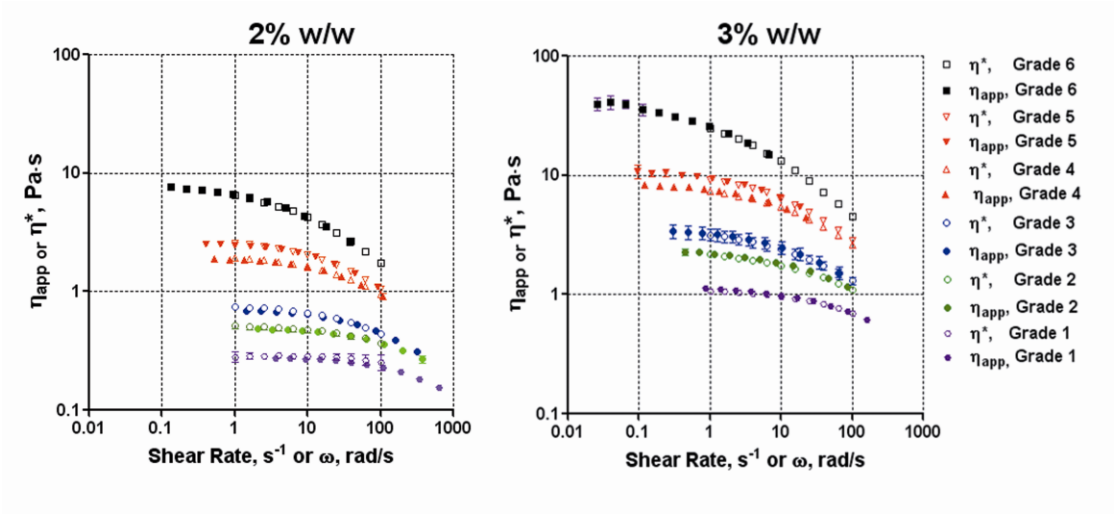

Figure 18. Complex viscosity (η^*) and apparent viscosity (η_{app}) as a function of angular frequency (rad/s) and shear rate (s^{-1}), respectively, for solutions of six grades of sodium alginate at 2% and 3% w/w and 25°C (solid symbols represent apparent viscosities; open symbols represent complex viscosities). Data are shown as mean and standard deviation of six replicates.

Concentration Effect on Viscoelasticity

The controlled release of drug substances from sodium alginate matrices was expected to correlate with the swelling and erosion behavior of the polymer matrix.[31,32] In the hydrated polymer layer, the alginate concentrations could range from very high values at the boundary with the unhydrated alginate, to relatively dilute concentrations at the boundary with the bulk alginate solution. Erosion of the hydrated polymer gel layer occurs at the boundary between sodium alginate gel and the bulk solution.[118] The *inter-*

and *intra*-polymer interactions involved in the erosion process are believed to be the same factors resisting strain under small amplitude oscillation measurements.[122] Therefore, the characterization of the rheological properties of sodium alginate solutions under small amplitude oscillation was extended to a wider range of sodium alginate concentrations in order to mirror the range of conditions that could be encountered in sodium alginate-based controlled release formulations during use.

The viscoelastic behavior of solutions of the various sodium alginate grades is typified by the data for grade 3 from 2% to 13% w/w, shown in Figure 19, which depicts the angular frequency (ω) dependence of G' and G'' of these solutions at 37°C — the temperature that peroral alginate formulations would be exposed to in the alimentary tract. At low concentrations, from 2 to 4 % w/w, liquid-like or fluid behavior is observed as G'' is higher than G' at the accessible angular frequencies and both G' and G'' are showing higher dependence on angular frequency than at higher concentrations. As sodium alginate concentrations increase beyond 4% w/w, G'' is still higher than G' at lower frequencies, but crossover of G' and G'' is evident at ~ 90 rad/s for 5% w/w, ~ 40 rad/s for 6% w/w, and ~10 rad/s for 7% w/w solutions. Both G' and G'' show decreased dependence on angular frequency with increasing concentration. When the alginate concentration reaches 8% w/w, G' is equal to or higher than G'' over the entire frequency range. For solutions with concentrations higher than 8% w/w, G' is always higher than G'' over the entire frequency range and G' is almost parallel to G'' in the low frequency range – a typical solid-like behavior for gels.[145-148] The oscillation data show that with an increase in concentration, sodium alginate solutions change from “liquid-like” behavior to “solid-like” behavior.

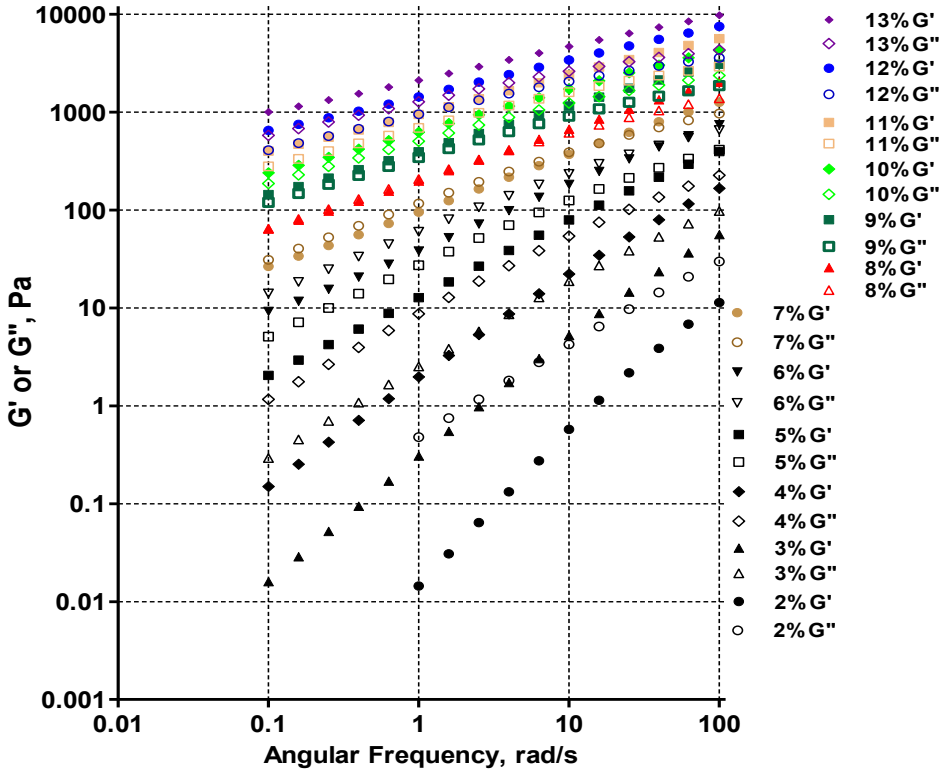

Figure 19. The G' and G'' as a function of angular frequency for sodium alginate (grade 3) solutions at different concentrations at 37°C.

For sodium alginate solutions at moderate concentrations, *i.e.*, from 5 to 7% w/w, G'' is greater than G' at low frequencies. This is most likely the result of the polymer chains having sufficient time to disentangle and flow during a single oscillation.[125] At high frequencies, G'' is smaller than G' due to insufficient time for the temporarily entangled polymer chains to come apart during a single oscillation, thereby resulting in the system's solid-like behavior.[125] Therefore, the lifetime or the relaxation time of the entangled polymer chains determines whether the system behaves as a solid or as a liquid in a particular frequency range. When the lifetime of the interchain entanglements is

longer than the time scale of observation ($1/\omega$), a solid-like behavior is obtained. The crossover frequency, *i.e.*, G' equals G'', corresponds to the average relaxation time of entanglements.[33,125] Therefore, the concentration at which G' equals G'' [and tan δ =1] in the lower end of the accessible frequency range (*e.g.*, 1 rad/s) can be considered to be the critical concentration at which the polymer solution becomes a gel.[147] For the sodium alginate (grade 3) solutions tested in this study, although both G' and G'' increase with increasing alginate concentrations, G' predominates relative to G'' once 8% w/w is reached. With concentrations higher than 8% w/w, G' parallels G'' in the lower frequency range while predominating in the higher frequency range. The concentration-dependence of sodium alginate solution viscoelasticity is further illustrated by the changing tan δ values with increasing concentrations, as shown in Figure 20. The tan δ values decrease with the increasing concentration and are less than 1 when the concentration exceeds 8% w/w over the entire angular frequency range.

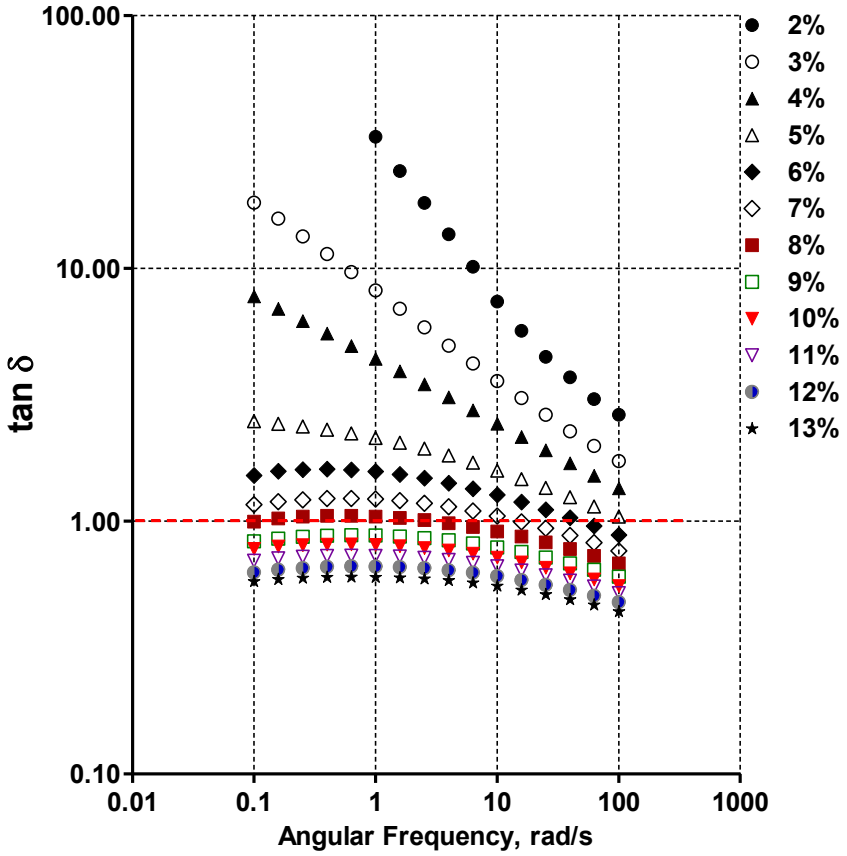

Figure 20. The tan δ as a function of angular frequency for sodium alginate (grade 3) solutions at 37°C.

The frequency dependence of G' and G'' can be characterized by the following power-law relationships:[149-152]

$$G' = K' \bullet \omega^{n'}, \qquad \text{Equation 24}$$

$$G'' = K'' \bullet \omega^{n''}, \qquad \text{Equation 25}$$

where K', K'', n', and n'' are constants.

The G' and G'' data for the grade 3 sodium alginate solutions were fitted by these two equations above and the fitted coefficients and exponents are summarized in Table 8.

Both K' and K'' values increase dramatically as sodium alginate concentration increases from 2% to 13% w/w. In the concentration range from 2% to 6% w/w, $K' < K''$ with the values of K' and K'' being very small, indicating a low degree of chain interaction and predominantly viscous behavior. With alginate concentrations changing from 6% to 7% w/w, there is a > 20-fold and >18-fold increase in K' and K'', respectively. The substantial increases in K' and K'' values suggest a dramatic augmentation in polymer chain interaction. As alginate concentrations are increased from 7% to 8% w/w, both K' and K'' exhibit a ~20-fold increase. A further increase in alginate concentration from 8% to 9% results in a further increase in K' and K''. However, the increases are < 6-fold. K' is slightly less than K'' at both 7% and 8% w/w but becomes larger than K'' at 9% — an indication of predominantly elastic behavior at the higher concentration. Therefore, based on the data for G' and G'', K' and K'', and tan δ as a function of alginate concentration, the critical transition point from a fluid to a gel state for sodium alginate (grade 3) solutions is approximately 8% w/w.

Table 8. Calculated power-law coefficients and exponents (reported as 95% confidence intervals of three replicates) of G' and G'' for sodium alginate (grade 3) solutions at different concentrations at 37°C.

Concentration, %w/w	K′	n′	R^2	K″	n″	R^2
2	(3.51 – 6.03) x 10^{-6}	1.13 – 1.25	0.999	(5.85 – 7.28) x 10^{-5}	0.81 – 0.86	0.999
3	(1.64 – 2.11) x 10^{-4}	0.96 – 1.02	0.999	(1.04 – 1.31) x 10^{-3}	0.69 – 0.74	0.998
4	(2.91 – 3.70) x 10^{-3}	0.83 – 0.88	0.999	(1.11 – 1.42) x 10^{-2}	0.60 – 0.66	0.997
5	(4.69 – 5.49) x 10^{-2}	0.68 – 0.72	0.999	(0.99 – 1.24) x 10^{-1}	0.51 to 0.57	0.996
6	(4.20 – 4.80) x 10^{-1}	0.60 – 0.63	0.999	(6.63 – 8.21) x 10^{-1}	0.45 to 0.51	0.995
7	(1.00 – 1.12) x 10^{1}	0.53 – 0.55	0.999	(1.23 – 1.50) x 10^{1}	0.41 – 0.46	0.994
8	(2.05 – 2.25) x 10^{2}	0.48 – 0.50	0.998	(2.14 – 2.56) x 10^{2}	0.37 – 0.42	0.993
9	(1.27 – 1.36) x 10^{3}	0.43 – 0.45	0.999	(1.10 – 1.30) x 10^{3}	0.33 – 0.38	0.993
10	(6.36 – 6.85) x 10^{3}	0.40 – 0.42	0.999	(5.03 - 5.89) x 10^{3}	0.31 – 0.35	0.992
11	(3.02 – 3.20) x 10^{4}	0.37 – 0.39	0.999	(2.16 – 2.50) x 10^{4}	0.29 – 0.33	0.992
12	(1.45 – 1.52) x 10^{5}	0.35 – 0.36	0.999	(0.93 – 1.07) x 10^{5}	0.27 – 0.31	0.991
13	(6.72 – 7.00) x 10^{5}	0.32 – 0.33	0.999	(3.93 – 4.66) x 10^{5}	0.25 – 0.29	0.990

Values of n' and n'' decrease gradually as alginate concentrations increase, indicative of a weaker dependence of G' and G'' on angular frequency at higher concentrations. It has been reported that a covalently crosslinked gel will have n' value ≈ 0 while a physically crosslinked gel would have $n' > 0$. For covalently crosslinked gel, the bonds are permanent and the mechanical behavior of the gels does change with the observation time, *i.e.*, the angular frequency. On the other hand, the bonds involved in physical gels are not permanent and the mechanical behavior of physically crosslinked gel is usually dependent on observation time and the relaxation time of the chain entanglements.[151-154] For sodium alginate solutions with concentrations from 8% to 13% w/w, the n' values vary from 0.49 to 0.33, suggesting a weak physical gel behavior due to extensive polymer chain entanglements. Additional support for the characterization of these alginate solutions as weak physical gels at concentrations from 8% to 13% w/w is provided by the slight dependence of tan δ on angular frequency[34] as shown in Figure 20.

The viscoelastic parameters of solutions of all the six grades of sodium alginate with increasing concentration are illustrated in Figure 21, which depicts the concentration dependence of the complex viscosity (η^*), storage modulus (G'), and tan δ of these sodium alginate solutions at 37°C.

The η^* and G' values increase with increasing concentrations for all six grades, representing an increased degree of chain entanglement. Grades 1 and 6 exhibit the lowest and highest viscoelastic parameters over the concentration range investigated. It is noted that viscoelastic parameters, *e.g.*, η^* and G', of grade 4 solutions are larger than those of grade 5 solutions at concentrations higher than 4% w/w, in contrast to the rheological behavior seen in their solutions at lower concentrations (2%, 3% w/w). Values of η^* and G' for Grade 4 are higher than those of grades 2, 3, and 5 over the whole concentration range, while the η^* and G' values for grades 2, 3, and 5 overlap each other at concentrations higher than 8% w/w. The tan δ values decrease with increasing concentrations and reach a value of one at different concentration for these six grades, indicating that these sodium alginate solutions change from the fluid state to the gel state with increasing concentrations due to increasing polymer chain entanglements. The transition from a polymer solution to a polymer gel occurs at the critical concentration, *i.e.*, when tan δ = 1.[145,146] Critical concentrations for all of the alginate grades were estimated to be ~ 11 %, 8 %, 8 %, 8 %, 10 %, and 5 % w/w, respectively, for grades 1 – 6, calculated from nonlinear regression fitting of tan δ vs. concentration data.

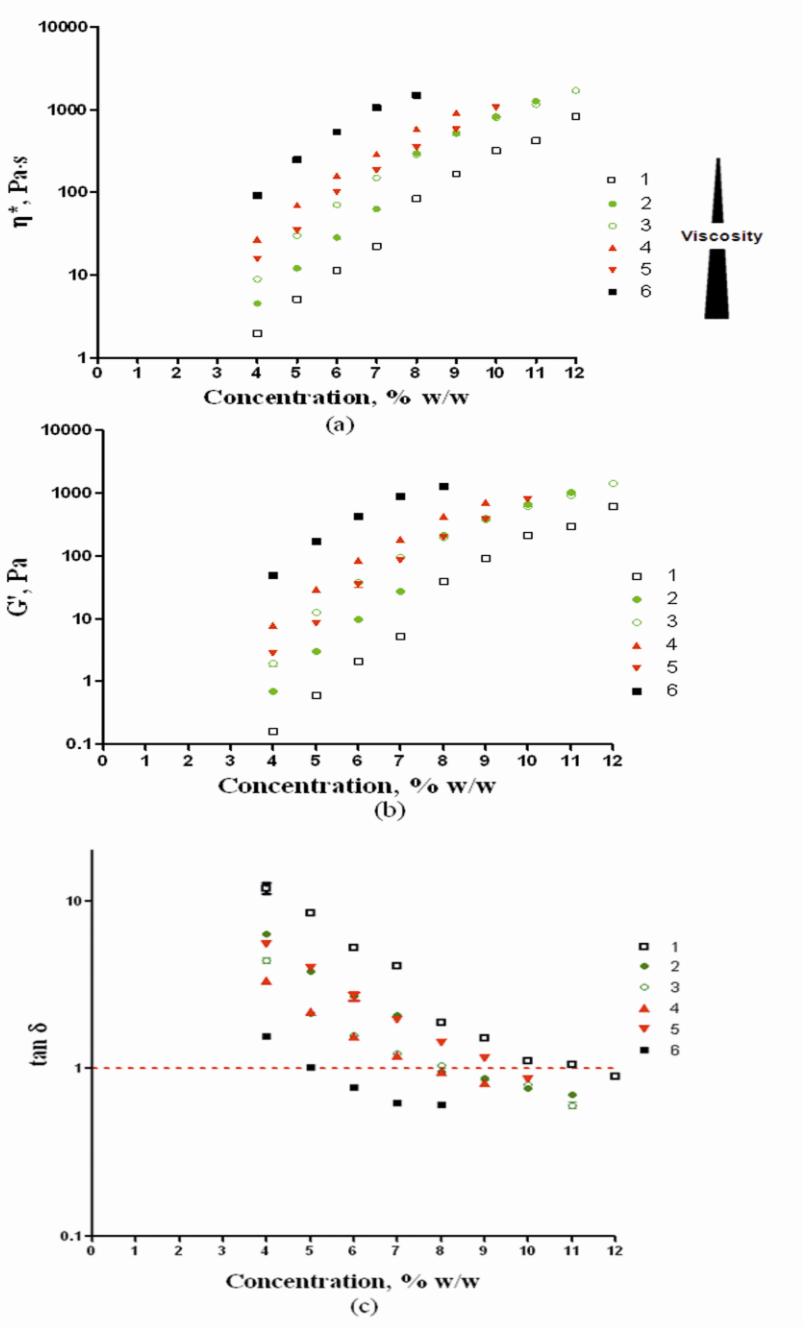

Figure 21. Concentration dependence of viscoelastic parameters (determined at 1 rad/s) of the solutions of sodium alginate (six grades) at 37°C: (a) complex viscosity (η^*); (b) storage modulus (G'), and (c) tan δ. Data are shown as mean and standard deviation of three replicates.

Generally, for linear polymers, the higher the molecular weight, the larger the degree of chain entanglement at high concentrations and the lower the critical concentration.[118] However, in this study, grades 2, 3, and 4 are substantially different in their molecular weight, but similar in their critical concentration. Grade 5, which is relatively high in both molecular weight and %G, shows higher tan δ values (and higher critical concentration) than grades 2 and 3. Although grades 4 and 5 are not significantly different from each other in viscoelasticity at lower concentrations, *i.e.*, 2% and 3% w/w, their viscoelasticity profiles at higher concentrations are significantly different from each other. Since the *G* sequence has the most rigid and extended chain conformation in solution among the three sequences,[58-60] sodium alginates with higher %G may have a coil conformation with lower degree of chain entanglement at high concentrations than those with a lower %G. Furthermore, grade 5 has a substantially lower residual calcium content than grades 2, 3, and 4 (Table 6). Although the calcium content for all these grades are relatively low and are not sufficient to form calcium alginate gels, there could be some interactions between calcium cations and sections of sodium alginate molecules, forming gel regions of limited size as well as quasi gel regions, especially at high alginate concentrations. The lower residual calcium content of grade 5 may result in fewer regional calcium alginate interactions and hence lower viscoelasticity than grades 2, 3, and 4 at high concentrations. In summary, the viscoelasticity of the various grades of sodium alginate at lower concentrations, is not indicative of their viscoelasticity profile at higher solution concentrations.

Apparent viscosities of solutions of multiple grades of sodium alginate at lower concentrations are not indicative of the viscoelastic properties of sodium alginate

solutions at higher concentrations, as well. Apparent viscosity at low concentrations is mainly determined by the interactions among polymers with relatively higher molecular weight in the polydisperse mixture. Viscoelasticity at high concentrations, especially when the concentration exceeds the critical concentration, is determined by the polymer interactions in a 3-D entangled network. Every polymer molecule in the polydisperse mixture is believed to be involved in the 3-D entangled network. As a result, it is not surprising that apparent viscosities at low concentrations may not be indicative of the viscoelasticity of sodium alginate solutions at high concentrations.

The pharmaceutical grades of sodium alginate, as with most polymeric pharmaceutical excipients, are grouped based on the apparent viscosity of their solutions at low concentrations, *e.g.*, 1% w/v. In fact, in most studies of sodium alginate matrices in the literature, only the "one-point" apparent viscosities of low concentration sodium alginate solutions were characterized.[31,32,75,155] More likely than not, the incomplete rheological characterization of sodium alginate solutions is responsible for the disparity among different studies on the significance of the influence of the viscosity grade of the polymer on drug release from alginate matrices.[31,32,75,155] A rational approach to QbD requires a more complete understanding of the rheological behavior (apparent viscosity and viscoelasticity) of these polymeric excipients as a function of excipient concentration and mechanical condition appropriate to the processing and performance of pharmaceutical formulations. For example, for sodium alginate used in extended release matrix tablets, it is reasonable to characterize both the apparent viscosity of sodium alginate solutions at relatively low concentrations and the viscoelasticity of sodium alginate solutions at relatively high concentrations.

Inter-Batch Variability

The following data reflect the evaluations of the one grade (grade 3) that was available in multiple batches.

Calcium Content, Chemical Composition, and Intrinsic Viscosities

The residual calcium content, chemical composition, and intrinsic viscosity ([η]) data for the ten batches of grade 3 are listed in Table 9. The residual calcium content of the sodium alginates employed in this study varies from 0.36% to 0.73% w/w. The corresponding molar ratios of calcium to sodium alginate monomer of the multiple batches range from 0.018 to 0.036, which is below the critical ratio (*i.e.*, 0.05) for calcium to exert significant effect on the rheological properties of aqueous alginate solutions.[134] The %G values of the multiple batches as determined in our laboratory range from 37 to 41%, within the range specified by the manufacturer. Intrinsic viscosities of the ten batches vary from 6.53 to 7.80 dL/g. Batch *A*, which has the lowest "one-point" viscosity value according to CoA, shows the highest intrinsic viscosity and average molecular weight in our study.

Table 9. Calcium content, %G, [η], and average molecular weights calculated based on intrinsic viscosities of the ten batches of sodium alginate grade 3. Mean and standard deviation were calculated from three replicates.

Batch	Calcium content,% (Mean ± S.D.)	%G per SSNMR (% Range)	[η] (dL/g) (Mean ± S.D.)	M_w (kDa) (Average)	M_n (kDa) (Average)

A	0.69 ± 0.010	37-41	7.80±0.20	373	97
B	0.73 ± 0.006	38-41	7.14±0.07	341	89
C	0.42 ± 0.008	38-41	7.32±0.18	350	91
D	0.62 ± 0.009	38-40	7.48±0.11	357	93
E	0.54 ± 0.002	38-41	6.67±0.12	318	83
F	0.55 ± 0.012	37-41	6.87±0.27	328	85
G	0.56 ± 0.008	39-41	6.53±0.39	311	81
H	0.45 ± 0.006	38-40	6.91±0.29	330	86
I	0.36 ± 0.008	39-42	7.33±0.19	350	91
J	0.41 ± 0.006	39-42	7.16±0.09	342	89

Steady Shear and Small Amplitude Oscillation

The inter-batch variability of grade 3 was determined by comparing the apparent viscosities of 2% w/w solutions of the various batches at 25°C. The inter-batch variability was further investigated by comparing the viscoelastic parameters of the various batch solutions at 8% w/w at 37°C, based on the earlier determination of the critical concentration for grade 3. The apparent viscosities of sodium alginate solutions at 2% w/w are depicted in Figure 22. ANOVA and the subsequent multiple comparisons tests demonstrate that batch *A* is significantly ($p < 0.001$) different from all other batches in

apparent viscosities of 2% w/w solutions while other batches are not significantly ($p > 0.05$) different in their apparent viscosities.

In contrast to the viscosity data provided in the certificates of analysis (CoA) in which batch *A* had the lowest viscosity value (Table 5), batch *A* exhibits substantially higher apparent viscosities than the other batches, which is in accordance with its having highest average molecular weight among the 10 batches. However, there is only one apparent viscosity value reported in the CoA for each batch. The CoA does not indicate when the apparent viscosity was measured with respect to the time of manufacture of each batch. Furthermore, since no standard deviation of apparent viscosity for each batch is supplied in the CoA, it is rather difficult to assess the variability of multiple batches. Excipient manufacturers usually have much more data on their excipient than those reported in the CoA, *e.g*., apparent viscosity data for sodium alginate solutions during extraction process, at different time points, etc. It is important for the formulation scientists to communicate well with the excipient manufacturer to gain the access to the manufacturer's database. In this way, formulation scientist could gain a better understanding of the variability of excipients under consideration.

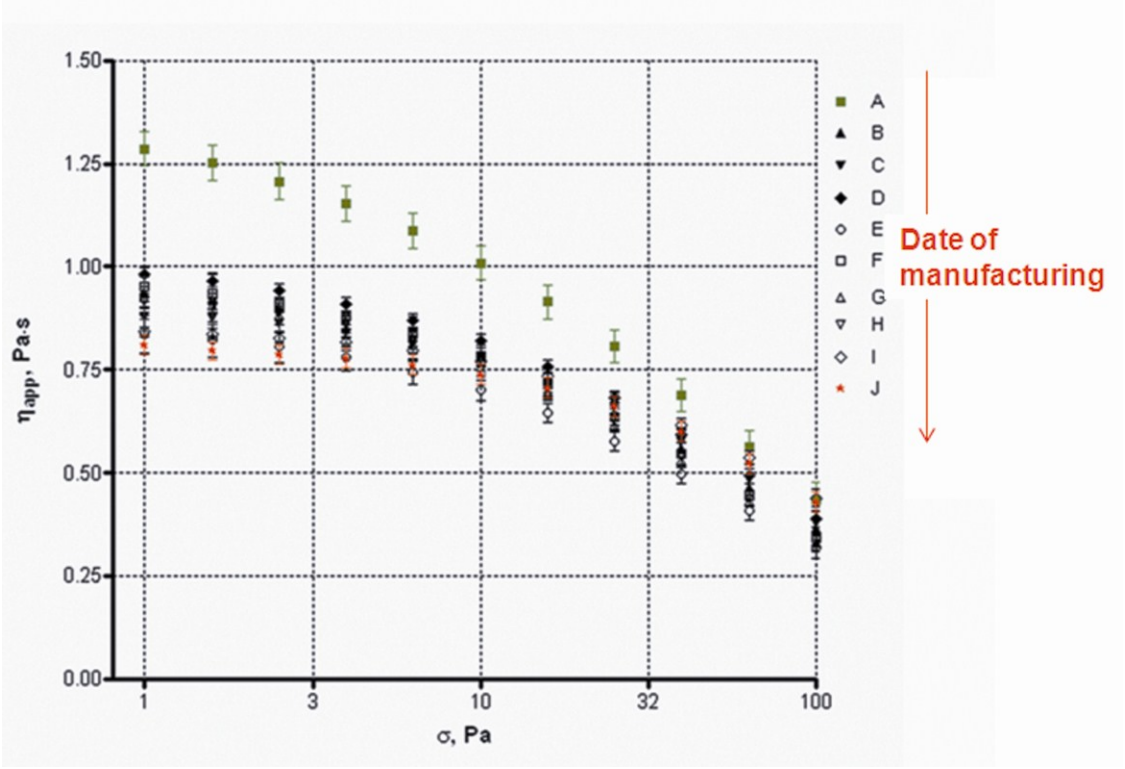

Figure 22. Steady shear result of sodium alginate (ten batches of grade 3) solutions at 2% w/w at 25°C. Data are shown as mean and standard deviation of six replicates.

The tan δ as a function of angular frequency for 2% w/w solutions of multiple batches at 25°C is depicted in Figure 23. Based on ANOVA, significant differences in tan δ among the ten batches are evident ($p < 0.001$). *Post hoc* multiple comparisons test indicated that more batches are significantly different in tan δ than in η_{app} (Table 10). In addition, those batches that are significantly different in η_{app} are not necessarily significantly different in tan δ.

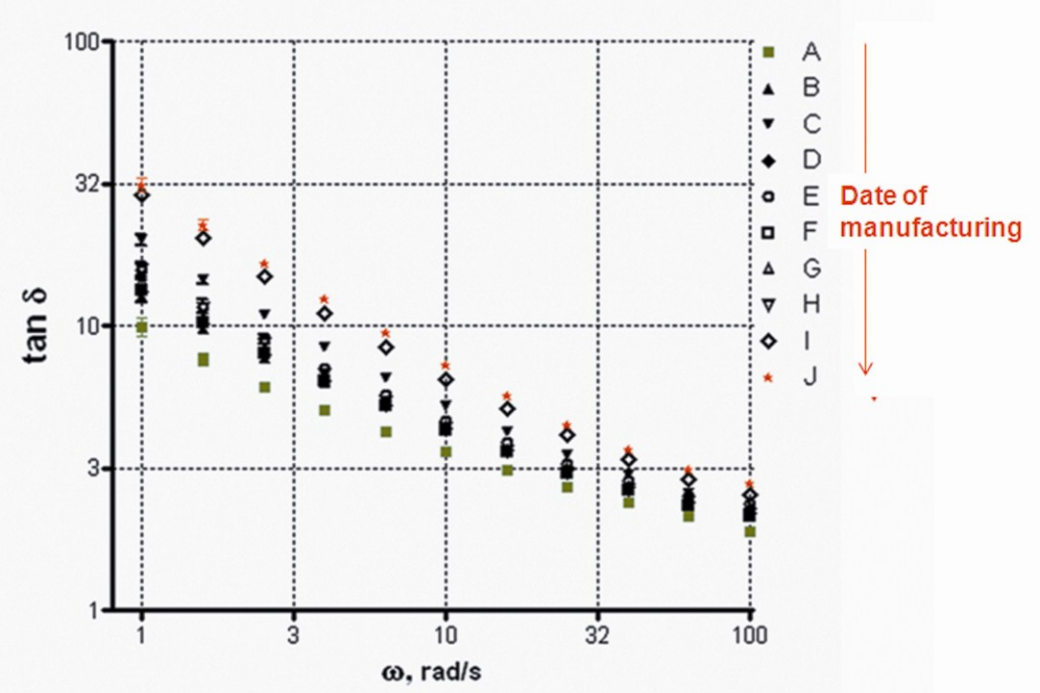

Figure 23. Angular frequency (ω) dependence of tan δ of the 2% w/w solutions of sodium alginate (ten batches of grade 3) at 25°C. Data are shown as mean and standard deviation of six replicates.

Figure 24 depicts tan δ of the solutions of multiple batches (8% w/w) over a wide range of angular frequencies at 37°C. Based upon ANOVA, significant differences ($P < 0.001$) among these multiple batches in tan δ are evident. The result of the *post hoc* multiple comparisons test for rheological parameters is summarized in Table 10. Batches showing significant differences in their η_{app} or tan δ at 2% w/w also demonstrate significant differences in their tan δ at 8% w/w. Furthermore, there are more batches showing significant differences in their tan δ at 8% than at 2% w/w. These outcomes are consistent with the likelihood of higher chances of inter-chain interactions at high concentrations. Inter-chain interactions are influenced by the differences in molecular

weight and chemical composition (influencing sodium alginate molecular chain mobility). These differences among multiple batches are evident in their viscoelastic properties. Batches *J* and *I*, which have the lowest viscoelasticity, also have the lowest residual calcium content among the ten batches. However, batch *H* has slightly higher residual calcium content than batch *J* but much higher viscoelasticity (as reflected in its lower tan δ values) than batch *J*. Hence, the effect of residual calcium content on the viscoelastic properties appears to be trivial.

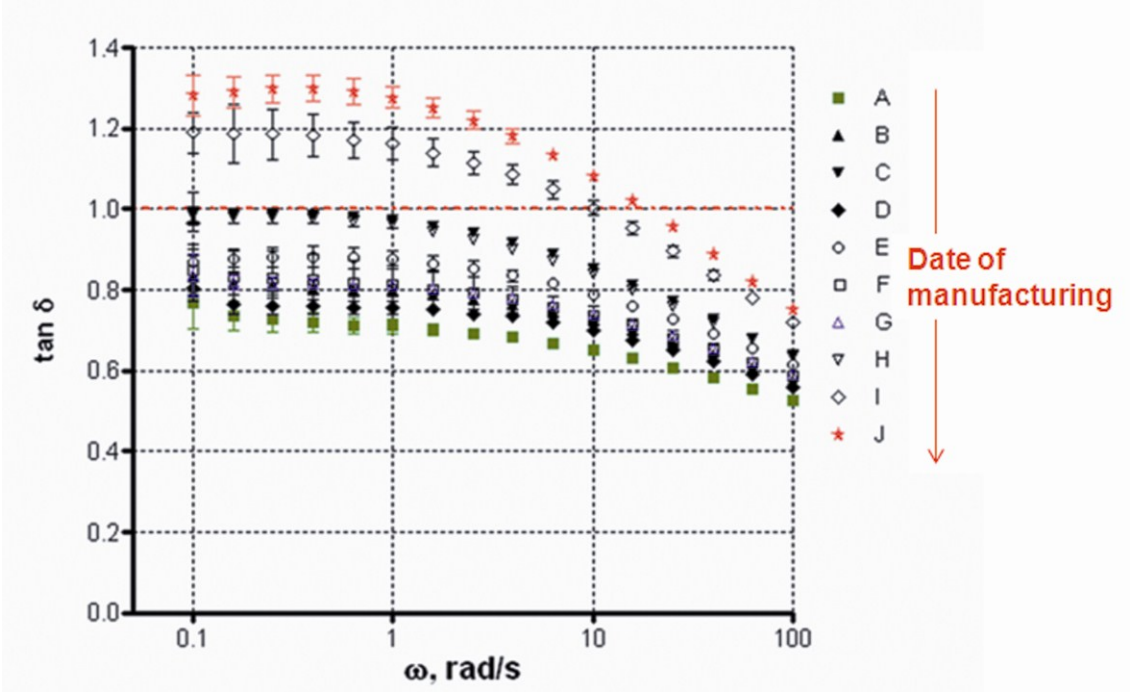

Figure 24. Angular frequency dependence of tan δ of the 8% w/w solutions of sodium alginate (ten batches of grade 3) at 37°C. Data are shown as mean and standard deviation of six replicates.

Table 10. Results for multiple comparisons test of the rheological parameters of the solutions of the ten batches of sodium alginate (grade 3).

Batch										
A	**A**									
B	η,Δ	**B**								
C	η,δ,Δ	Δ	**C**							
D	η,Δ	—	Δ	**D**						
E	η,Δ	Δ	Δ	Δ	**E**					
F	η,Δ	—	Δ	Δ	Δ	**F**				
G	η,Δ	—	Δ	Δ	Δ	—	**G**			
H	η,Δ	Δ	—	Δ	Δ	Δ	Δ	**H**		
I	η,δ,Δ	δ,Δ	Δ	δ,Δ	Δ	δ,Δ	δ,Δ	δ,Δ	**I**	
J	η,δ,Δ	δ,Δ	Δ	δ,Δ	δ,Δ	δ,Δ	δ,Δ	δ,Δ	Δ	**J**

The symbols in the cells correspond to significant differences in the paired data for specific rheological outcomes, as follows:

$\eta = \log \eta_{app}$ (2% w/w, 25°C); $\delta = \tan \delta$ (2% w/w, 25°C)

$\Delta = \tan \delta$ (8% w/w, 37°C); — = No significant differences

In summary, batch *A* shows significantly higher apparent viscosity than other batches at 2% solution, while other batches are similar in their apparent viscosity. More batches are showing significant differences in viscoelastic properties of their solutions. Batches *I* and *J* are significantly different from other batches in viscoelasticity. It seems that the variability of multiple batches could be related to their date of manufacturing. A

further investigation on the manufacturing time-dependent variability was conducted and is presented below.

Inter-Batch Variability as a Function of Date of Sodium Alginate Manufacture

Figure 25 depicts the variations in $[\eta]$, η_{app} (2% w/w, σ = 1 Pa, 25°C), tan δ (2% w/w, ω = 1 rad/s, 25°C), η^*, G', and tan δ (8% w/w, ω = 0.1 rad/s, 37°C) as a function of time. The largest differences in the rheological parameters are evident between the batch produced in January and the last two batches produced in October and November. Batches manufactured between February and September show relatively small variations in their rheological behavior. Since alginates occur as a structural component in seaweed, the seasonal tidal fluctuations would lead to different degrees of seaweed stiffness and, therefore, variations in chemical composition and molecular weight of alginates. Furthermore, the ratio of actively-growing (young) to resting (old) tissue also varies in different seasons, resulting variation in alginate molecular structure.[156] Thus, the season of harvesting may well be a factor contributing to the batch-to-batch variability of sodium alginate.

Personal discussions with Dr. Brian Carlin from FMC Biopolymer indicate that the inter-batch variability of sodium alginate in chemical composition and viscosity was minimized by using— as the source material— a mixture of seaweeds harvested in different months during the year. Results obtained in this study did show that %G values of multiple batches produced in the same year fall within a narrow range and meet the specification set by the manufacturer. In addition, the "one-point" viscosity data of the multiple batches reported in the CoA showed that all these batches are within a very

narrow range and meet the manufacturer's specification. However, the results in our study demonstrated that these batches still exhibit significant differences in their rheological behavior at concentrations higher than 1% w/w. Thus, reliance on "one-point" viscosity data to minimize inter-batch variability is potentially misleading. The inter-batch variability could be better controlled by adjusting the viscoelastic properties of sodium alginate solutions during the extraction process. The processing parameters in several extraction steps, such as acid treatment, alkaline extraction, conversion of calcium alginate to alginic acid, and conversion of alginic acid to sodium alginate, can be adjusted to achieve sodium alginate solutions at the last step within a specified range of viscoelasticity. The specific range of viscoelasticity will need to be explored and defined for a specific grade in order to achieve the desired batch-to-batch variation.

On the other hand, there is no simple answer to the question that how much impact of the batch-to-batch variability of sodium alginate, or any other excipients, on the performance of the final products. It will depend on the functionality and the percentage of the excipient in a specific pharmaceutical product. Hence, it is critical for pharmaceutical formulation scientists to determine the impact of the batch-to-batch variability of excipients on the performance on the drug products under development. An acceptable level of batch-to-batch variability should be defined. The next step would be to communicate with the excipient supplier to ensure that the acceptable variability is achievable in the manufacturing process. In case the acceptable variability is very narrow, it might not be practical for the excipient manufacturer to supply multiple batches within the specification. A modification to the formulation may be necessary to avoid this issue.

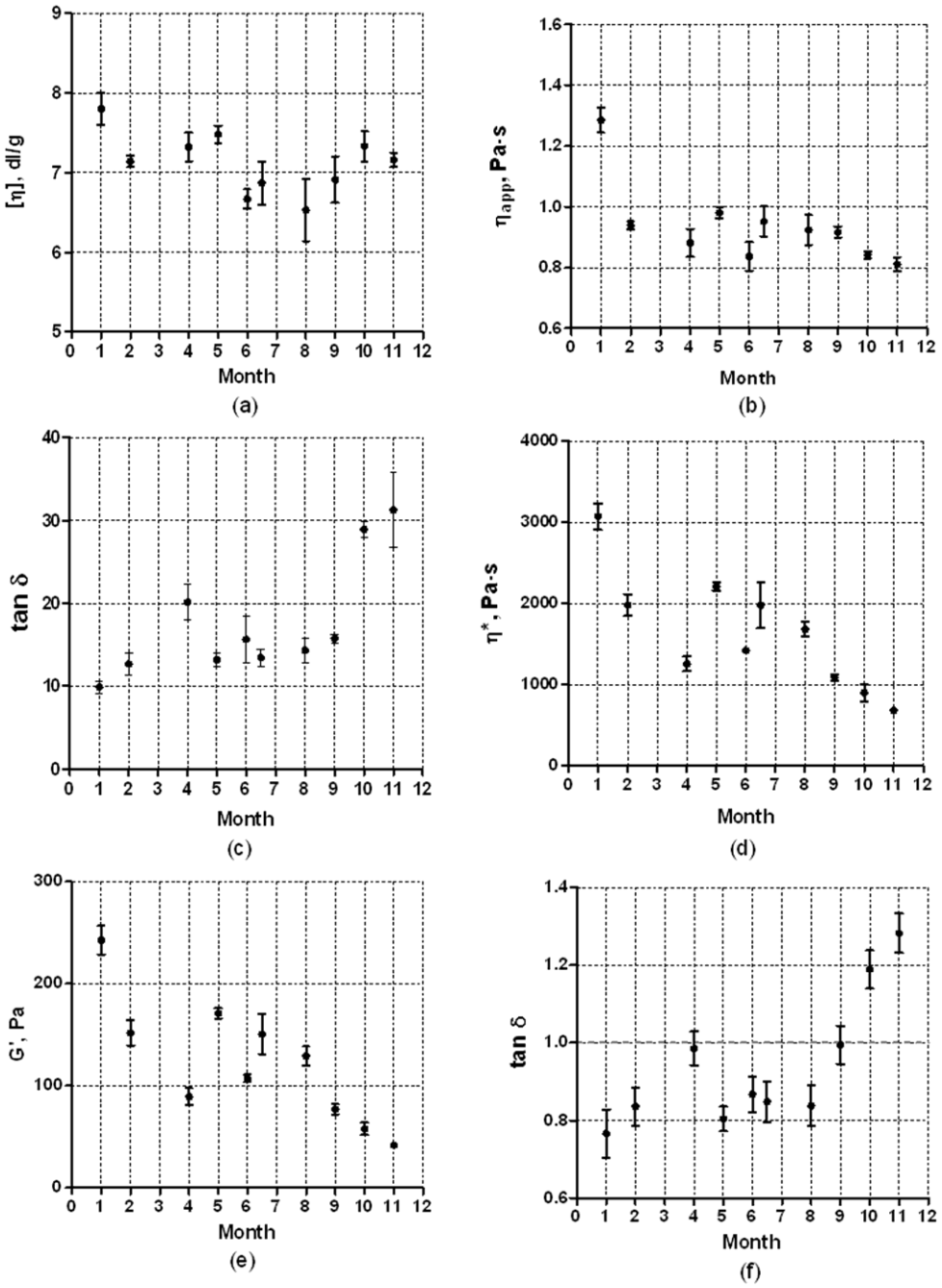

Figure 25. Temporal variations in rheological parameters of the solutions of multiple batches of grade 3: (a) [η]; (b) η_{app} (2% w/w, σ = 1 Pa, 25°C); (c) tan δ (2% w/w, ω = 1 rad/s, 25°C); (d) η*; (e) G′; and (f) tan δ (8% w/w, ω = 0.1 rad/s, 37°C). Error bars represent the standard deviation of each parameter (n = 3).

Temperature Effect on Apparent Viscosity and Viscoelasticity

The temperature influence on the viscosity and viscoelasticity of sodium alginate solutions was also investigated in this work. At the outset, the effect of temperature on solutions of one grade (grade 3) of sodium alginate at different concentrations was investigated. Steady shear results for sodium alginate solutions at two different temperatures (20 and 37°C) are illustrated in Fig. 26. The apparent viscosities at 37°C are significantly lower than at 20°C (Table 11). That's mainly because at higher temperature, the friction energy among polymer chains and polymer-solvent is smaller than that at lower temperature. Thus, when comparing the viscosity values of different grades or batches of sodium alginates in solution, it is important to make sure that the viscosity data were collected at the same temperature.

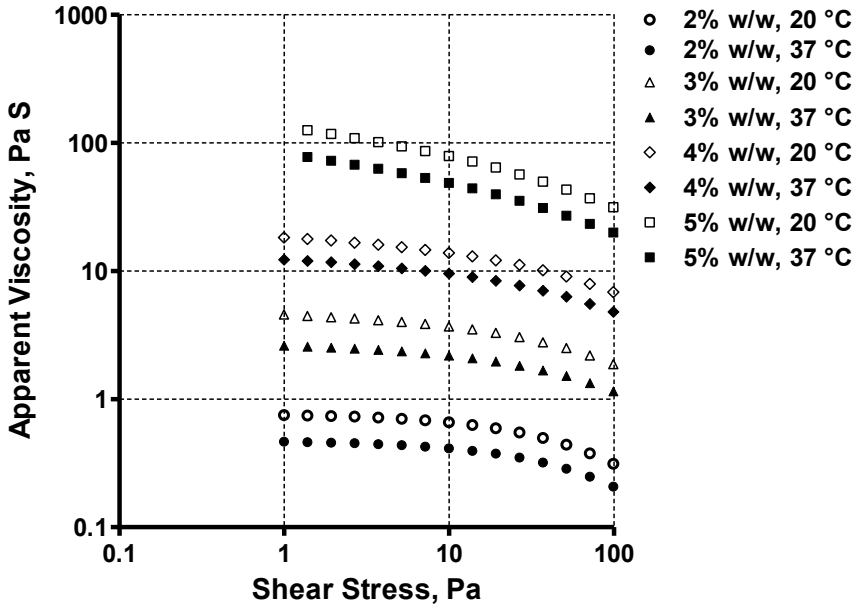

Figure 26. Temperature effect on sodium alginate (grade 3) solutions at various concentrations.

Table 11. One-way ANOVA test results for steady shear data of sodium alginate (grade 3) solutions at two different temperatures.

Concentration, % w/w	**p Value (log Apparent Viscosity, 20°C vs. 37°C)**
2	< 0.001
3	< 0.001
4	< 0.001
5	< 0.001

SAO studies have also been conducted on aqueous solutions of grade 3 sodium alginate at various concentrations at two different temperatures: 20 °C and 37 °C. Fig. 27 depicts tan δ as a function of angular frequency. SAO results indicate that, at each concentration, G' and G'' are slightly higher and tan δ slightly lower at the lower temperature (20°C) than at the higher temperature (37°C.). At first glance, an increase in temperature appears to reduce elasticity of sodium alginate solutions, to some extent. However, subsequent statistical evaluation of the viscoelasticity data with an ANOVA test suggests that temperature does not exert a significant influence on the viscoelasticity of sodium alginate solutions at relatively high concentrations (e.g., > 4% w/w), at least in the temperature range investigated (Table 12). At low concentrations (2% or 3%), higher temperature increases tan δ to some extent (decreasing viscoelasticity). It can be viewed as a horizontal shift of tan δ, *i.e.*, the same tan δ values are obtained at higher angular frequency at higher temperature. The observed viscoelasticity of sodium alginate solution is determined by the relaxation time of polymer entanglement and the observation time.

Increased temperature decreases the relaxation time of polymer entanglements. Thus, a higher angular frequency (smaller observation time) is required to obtain the same viscoelasticity, at least for sodium alginate solutions at low concentrations. Higher concentrations are associated with an increase in polymer chain interactions. The temperature effect on viscoelasticity is relatively minimal at high concentrations.

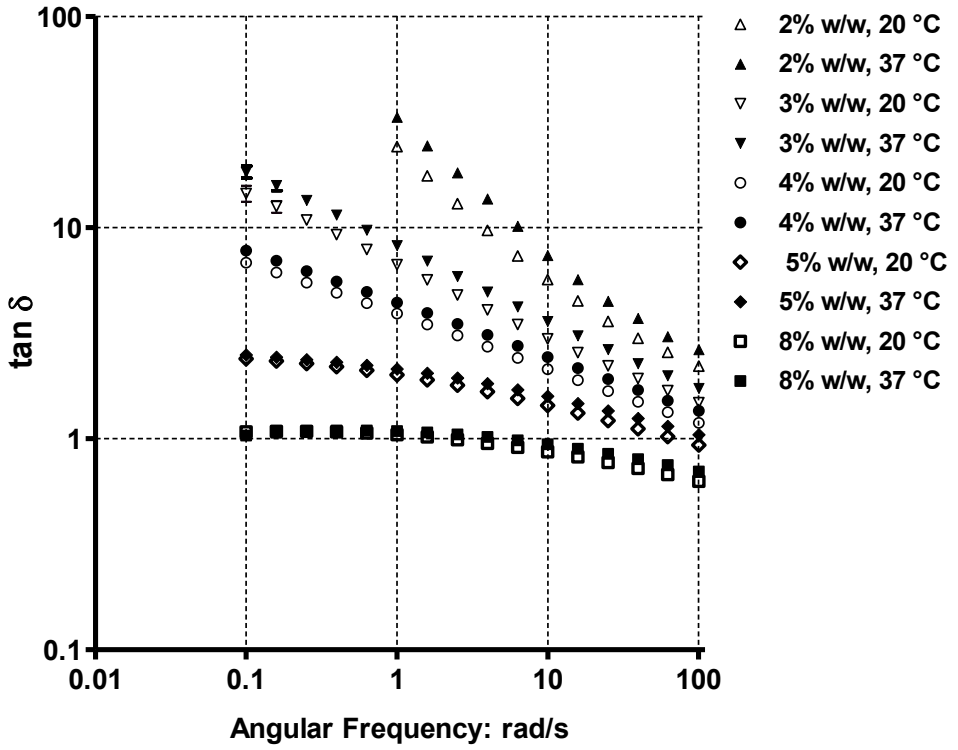

Figure 27. The tan δ as a function of angular frequency for sodium alginate (grade 3) solutions at various concentrations at both 20°C and 37°C.

Table 12. One-way ANOVA test results for viscoelastic data of sodium alginate solutions at two different temperatures.

Concentration, w/w	**P value (20°C vs. 37°C)**		
	tan δ	**log G'**	**log G''**

2%	0.15	0.19	0.20
3%	0.16	0.26	0.28
4%	0.24	0.39	0.44
5%	0.19	0.30	0.38
8%	0.12	0.22	0.25

Subsequently, a wider temperature range was investigated to ascertain the effect of temperature on the apparent viscosity of the six grades of sodium alginate in 2% w/w solutions. Temperature-dependent apparent viscosities of 2% w/w sodium alginate solutions are illustrated in Fig. 28. For each grade, apparent viscosity decreases with increasing temperature. However, the rank of apparent viscosity among the six grades of sodium alginate in 2% w/w solutions remains the same over the whole temperature range investigated. In Fig.28, temperature (K)-dependent viscosities of the six grades of sodium alginate solutions are fitted by the empirical equation:[157]

$$\eta = a \cdot \exp(\frac{b}{T}), \qquad \text{Equation 26}$$

where a (unit: Pa·s) and b (unit: K) are empirical constants. Calculated constants are summarized in Table 13. The large differences in a among the six grades are a reflection of their substantial differences in apparent viscosity of 2% w/w solutions at any specific temperature within the range of 15-45 °C. The relatively small variation in b corresponds to the similarity of temperature-dependence of apparent viscosity for the six grades of sodium alginate in solution. The rank order of these six grades does not change at various temperatures. On the other hand, the absolute apparent viscosity values for each grade changes substantially with changing temperature. As a result, when comparing viscosity

data of solutions of sodium alginate from different sources, grades, and/or batches, it is very important to ensure that the viscosity data are obtained at the same temperature.

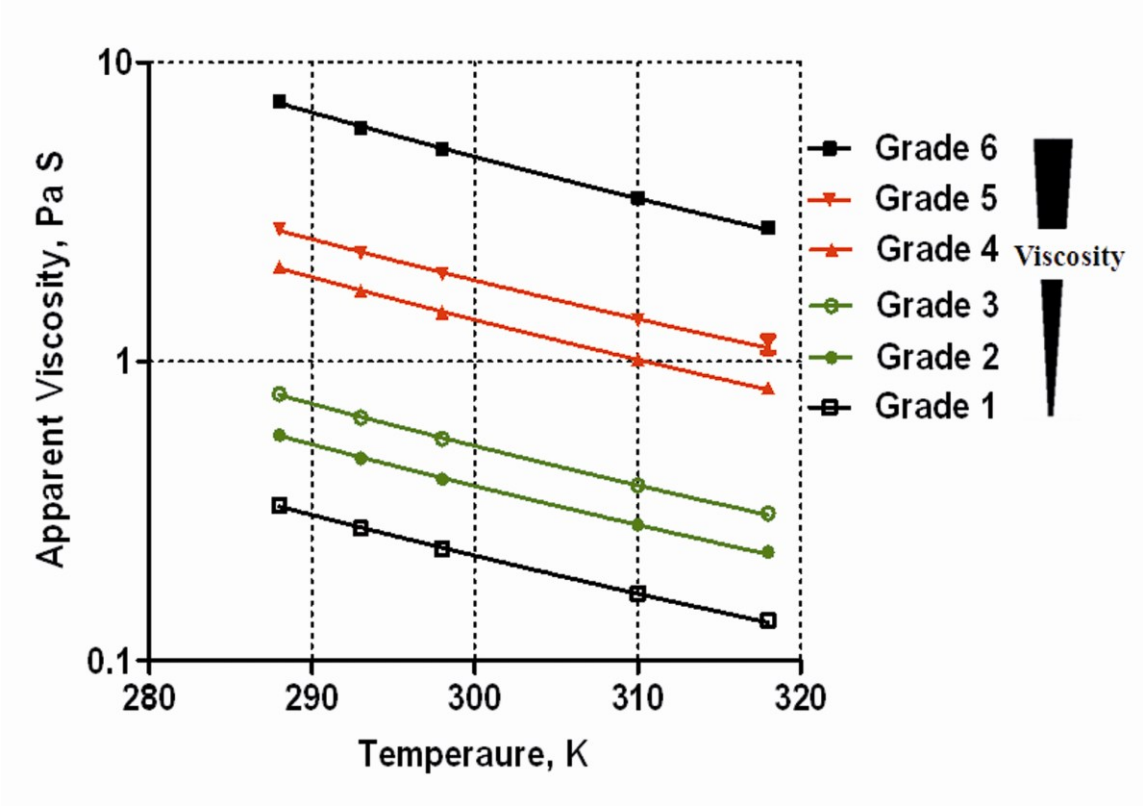

Figure 28. Apparent viscosity of the six grades of sodium alginate in 2% w/w solutions under 10 Pa shear stress as a function of temperature.

Table 13. Calculated constants and exponents of temperature-dependent viscosity.

Grade	a x 10^5 (Pa·s)	b (K)	R^2
1	2.54	2,727	0.999
2	3.59	2,783	0.999
3	4.34	2,819	0.999

4	10.27	2,852	0.993
5	18.81	2,761	0.981
6	23.99	2,973	0.998

In the final analysis, for sodium alginate used as a thickener or binder, it is recommended to characterize the sodium alginate solutions using steady shear measurements over a relatively wide range of shear stresses or shear rates. The resultant apparent viscosities or rheograms could be used to ensure batch-to-batch, grade-to-grade, or supplier-to-supplier interchangeability of sodium alginate or to define the design space — in accordance with QbD principles — for specific formulations. For sodium alginate used in controlled release matrices, both steady shear (at one low concentration, *e.g.* 2% w/w) and small amplitude oscillation measurements (at one high concentration indicative of polymer gel state, *e.g.* 8% w/w) are recommended to be performed on sodium alginate solutions to ensure interchangeability or to define the design space.

Conclusion

Rheological properties of macromolecular excipients are important parameters that can be related to their functionality in different drug dosage forms and delivery systems. In this work, steady shear and small amplitude oscillation tests have been performed on solutions of six grades of sodium alginate at a wide range of shear stresses and angular frequencies, respectively. Steady shear results suggest that the apparent viscosities of solutions of different grades of sodium alginate are concentration and shear condition dependent. The differences in apparent viscosity among solutions of various grades of sodium alginate become more substantial at higher concentrations or lower

shear stress. Sodium alginates with higher molecular weight and higher %G are likely to exhibit higher solution viscosity at fixed concentration. When sodium alginate is used as a thickener or binder, the rheograms of its solutions at appropriate concentrations and shear conditions could be used as the basis for establishing the interchangeability and equivalence of multiple grades or batches from the same or different suppliers.

As sodium alginate solution concentrations are increased, the rheological behavior of the solutions changes from that of a liquid to that of a weak physical gel. When sodium alginate is used for alginate-based matrices, the viscoelastic properties of its solutions at higher concentrations are recommended to be employed among the criteria for including different grades of sodium alginate in the formulation of alginate-based matrices.

Rheological evaluations of multiple batches of one grade of sodium alginate produced over the course of one year showed significant batch-to-batch variability in rheological behavior at both low and high solution concentrations. Viscoelastic properties at one high concentration (8% w/w) are more indicative of the inter-batch variability than the rheological properties of solutions at lower concentrations.

While temperature significantly influences steady shear behavior of sodium alginate solutions — especially at higher temperatures — it does not markedly affect solution viscoelasticity at least in the temperature range from 15 to 40 °C.

The results of this study demonstrate that apparent viscosity and viscoelasticity of sodium alginate solutions enable the identification of inter-grade and inter-batch variability of sodium alginate. The results also emphasize the importance of characterizing the rheological behavior of solutions of sodium alginate at concentrations and conditions consistent with the relevant manufacturing processes and delivery system

environments. In this way one can justify the selection of an appropriate grade of sodium alginate for inclusion in a pharmaceutical formulation. Furthermore, viscoelasticity of sodium alginate solutions can be used as the criteria to control the batch-to-batch variability of a specific grade of sodium alginate within a narrow range.

CHAPTER 3. INTER-GRADE AND INTER-BATCH VARIABILITY OF SODIUM ALIGNATE USED IN ALGINATE-BASED MATRIX TABLETS

Part 1. Direct Compression Properties of Sodium Alginate

Tablets, the most commonly manufactured pharmaceutical products, are solid dosage forms made from powdered or granular materials by compression or, infrequently, by molding methods. Given the wide application of compressed tablets, it is important to understand the tableting behavior of the solids that are to be compressed into tablets in terms of their compressibility (the ability of a material to undergo reduction in volume under pressure) and compactibility (the ability of a material to yield a compact of adequate strength). Compressibility is usually studied by exploring the relationship between compact porosity and the applied pressure, using various mechanical models,[158-

[160] while compactibility is generally assessed by defining the relationship between the tensile strength of the compacts and the corresponding compact porosity.[161]

Pharmaceutical powder compression is a complex process. It consists of several overlapping stages such as particle rearrangement, elastic/plastic deformation, and fragmentation. Powders undergo rearrangement, sliding, and restacking without deformation at low pressures. With increasing pressure, fragmentation of primary particles may take place by brittle fracture. Consequently, the broken particles fill into small spaces between larger particles, leading to volume reduction. In addition to particle fragmentation, plastic deformation may take place as powder particles undergo irreversible deformation in response to the increasing pressure. In fact, fragmentation and plastic deformation occur with all materials, and it is the extent of the two processes taking place during compression that determines the volume reduction mechanism of a given material.[160] Furthermore, elastic deformation dominates at higher pressures where the porosity of the powder bed is significantly reduced (*e.g.*, when the porosity of the powder bed is < 10%) and the powder bed behaves like a solid body. It is a reversible deformation and is directly proportional to the magnitude of the applied pressure.

Compression behavior of pharmaceutical powders has been analyzed using several mathematical models describing the change in porosity or volume in a powder bed as a function of applied pressure originally derived in other fields of industry, *e.g.*, the Heckel analysis,[158,162] the Kawakita model,[159] and the Gurnham equation.[160,163] Parameters obtained from these models have been proposed as indicators of the primary consolidation mechanism of pharmaceutical powders.

Sodium alginate has been widely investigated as a filler-binder in matrix tablets for controlled drug release with a percentage of ~30% w/w of the tablet.[31,32,75,76,155] However, little information on the compression and compaction behavior of sodium alginate has been published. Schmid and Picker-Freyer evaluated the tableting properties of sodium alginate using a 3-D modeling technique encompassing density, time, and pressure of the material during compression.[164] The authors concluded that sodium alginate deformed elastically and its compression behavior was dependent on both G/M ratio and molecular weight.[164] Yet, in another study on the compression behavior of composite particles consisting of lactose and sodium alginate, Takeuchi *et al*, reported that the increased amount of sodium alginate in the composite particles led to an increase in plastic deformation, suggesting a plastic deformation mechanism for sodium alginate during compression.[165] There is also a lack of published data on the variability in compression behavior of multiple batches from the same grade of sodium alginate. Thus, more studies need to be performed to better understand the compression properties of various grades and batches of sodium alginate.

In this study, four grades of sodium alginate and three batches of a single grade were selected to study their compression properties. Compression behavior of sodium alginates may be influenced by particle size and molecular weight distribution according to Schmid and Picker-Freyer.[164] For the four grades included in this study, the reported average particle size is the same, *i.e.*, 75 μm. However, the particle size distribution among the four grades could be different, leading to different compression behavior. Generally, polymers with lower molecular weight tend to deform more plastically than polymers with higher molecular weight.[166] Molecular weight change of polymers in the

lower middle molecular weight range could lead to substantial change in their mechanical properties.[166] After reaching a threshold molecular weight, further increase will result in only minor changes in mechanical properties.[166] The M_w of the four grades of sodium alginate varies from 288 to 409 kDa and the M_w of the three batches varying from 311 to 373 kDa. There might be more differences among the grades than among the batches with respect to their compression behavior.

Buckner *et al*. demonstrated that the use of consolidation models in conjunction with a compaction energetics analysis is a more reliable approach to evaluating the relative plasticity of pharmaceutical materials.[167] For consolidation models, the out-of-die method is preferred because porosity data collected under pressure could be influenced by elastic deformation and true density variation.[168,169] In this study, the Gurnham and Heckel models were employed to analyze the out-of-die compression data of sodium alginate. In addition, the compaction energetics of sodium alginates were examined in accordance with Buckner *et al.*.[167,170]

Materials and Methods

Materials

Four grades (one batch each) and three batches of one grade of sodium alginate (LF120M, SA Grade 3) were provided by FMC Biopolymer (Drammen, Norway). Sodium alginate powders (passed through 125 μm sieve) were used for the compression studies. Physicochemical properties, previously determined for these grades and batches are listed in Table 14. Apparent viscosity of alginate solutions increases from grade 2 to grade 4. Multiple batches of sodium alginate were designated as batches *A* to *J* on the

basis of their date of manufacture, with batch A as the earliest batch. Microcrystalline cellulose (MCC, Avicel PH 102, FMC Biopolymer, Princeton, NJ, USA) and lactose anhydrous (Kerry Bio-Science, Norwich, NY, USA) were used for comparison in the compression studies.

Table 14. Viscosity specification by manufacturer, guluronic acid percentage (%G), and intrinsic viscosity of the four grades and three batches of sodium alginate used in the compression studies.

Sodium Alginate	FMC Product Name	Viscosity range[a] mPa·s	% G[b]	Intrinsic viscosity, [η], dL/g Mean ± S.D.[c]
SA Grade 2	Protanal LF240D	70-150	33 - 36	6.04 ± 0.09
SA Grade 3	Protanal LF120M	70-150	38 - 42	6.43 ± 0.06
SA Grade 4	Protanal LF200M	200-400	39 - 43	8.72 ± 0.24
SA Grade 5	Protanal LF200DL	200-400	48 - 52	8.54 ± 0.12
Batch A	19338	70-150	36-41	7.80 ± 0.20

Batch G	19961	70-150	35-40	6.53 ± 0.39
Batch J	20228	70-150	35-41	7.16 ± 0.09

a: Viscosity data reported in manufacturer's certificate of analysis [Viscosity of 1% w/v sodium alginate solutions at 20 ºC using a Brookfield viscometer, spindle #3 at 40 rpm].

b: %G was determined by solid-state NMR.

c: n=3.

Methods

Bulk Density and Tapped Density

Bulk density and tapped density of sodium alginate powders were determined according to USP32-NF27 <616> with 35 ± 1 g powder in 100 mL graduate cylinder.

Moisture Content

All sodium alginate powders were stored at room temperature (typically 20–22ºC) and controlled humidity (31-33% relative humidity) which was achieved with saturated magnesium chloride ($MgCl_2$) solution.[171] Moisture content of sodium alginate powders was determined according to USP <731> loss on drying method using Computrac® Moisture Analyzer Max-2000 (Arizona Instrument, Chandler, AZ, USA).

True Density

The true densities of sodium alginate powders were determined with a helium pycnometer (Quantachrome Instruments, Boynton Beach, Florida, USA).

Particle size distribution

The particle size distribution of the various sodium alginates was estimated according to the USP32-NF27 <786> agitation method using analytical sieves (125 μm, 75 μm, 53 μm, and 38 μm sieves).

Compaction

Compacts were prepared with an Instron Universal Testing Machine (model 5869) equipped with flat-faced punches and a 50 kN load cell (Instron, Norwood, MA, USA). Powders of 400 ± 1 mg were filled into a 12-mm cylindrical die and were compressed and decompressed at 1 mm/min up to a specified compression pressure ranging from 25 to 265 MPa. Instron-developed software, Bluehill®2, was used to operate the instrument and collect the force and displacement data during compression. Each experiment was conducted in triplicate. The punches and die were lubricated with a 2% (w/v) magnesium stearate suspension in methanol before each set of triplicates and allowed to dry. All powders and compacts were stored at room temperature (typically 20–22ºC) and controlled humidity (31-33% relative humidity) which was achieved with saturated magnesium chloride ($MgCl_2$) solution.[171]

Porosity of Matrix Tablets

Matrix tablet dimensions (diameter and thickness) were determined at 0, 24, 48, and 72 h after compression by using an electronic digital caliper (Marathon Ltd., Richmond Hill, Ontario, Canada). Tablet porosity (ε) was calculated according to Equation 27:

$$\varepsilon = 1 - \left(\frac{D_{apparent}}{D_{true}} \right) = 1 - \left(\frac{m}{0.25 \cdot \pi \cdot D^2 \cdot t \cdot \rho} \right), \qquad \text{Equation 27}$$

where m is the tablet weight, D is the tablet diameter, t is the tablet thickness, and ρ is the true density of the sodium alginate powder.

Tensile Strength

When the porosity of sodium alginate compacts ceased changing during storage, typically after 72 h, sodium alginate matrix tablets were diametrically compressed at 10 mm/min until fracture using Instron Universal Testing Machine (model 5869) equipped with a 1 kN load cell (Instron, Norwood, MA, USA). The fixture plates were covered with thin strips of paper to minimize shear stress at contact points. Tablets fractured diametrically into two equal halves. The tablet tensile strength (σ_T) was calculated according to the following equation:

$$\sigma_T = \frac{2 \cdot F}{\pi \cdot D \cdot t}, \qquad \text{Equation 28}$$

where F is the force required to fracture the tablets, D is tablet diameter, and t is tablet thickness.[172,173]

Data Analysis

Compaction Energetics

Compaction energetics at each compression pressure were calculated. Two mathematical models (Gurnham and Heckel models) were used to analyze the out-of-die compression data. Compression work and decompression work (elastic work) were determined through analysis of the area under the force-displacement (*F-D*) curves (Figure 29) obtained during the compression and decompression processes in accordance with Equations 29 and 30, respectively.

$$W_{compression} = \int_{0}^{max\ displacement} F \cdot dD, \qquad \text{Equation 29}$$

$$W_{decompression} = \int_{max\ displacement}^{final\ displacement} F \cdot dD, \qquad \text{Equation 30}$$

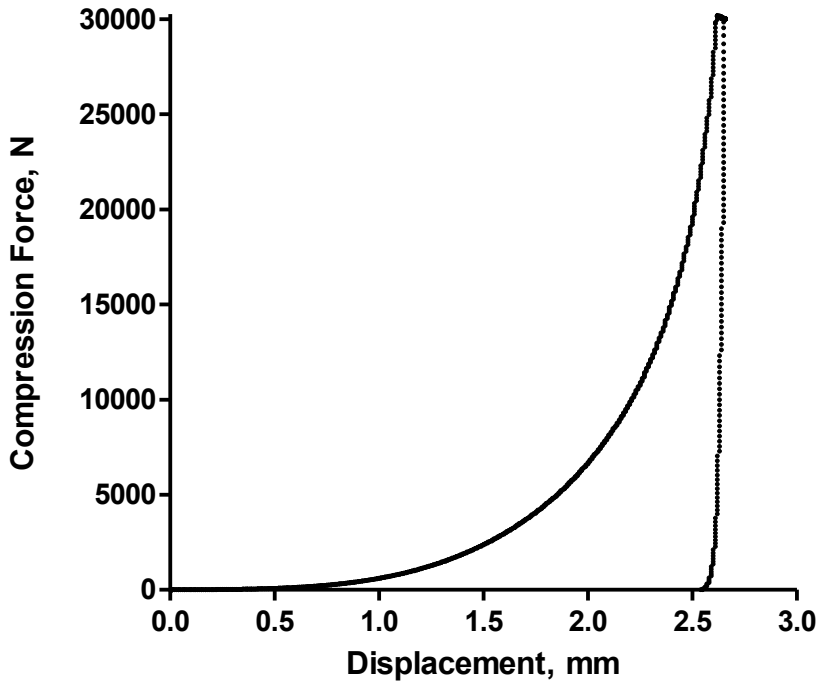

Figure 29. Typical compression profile of sodium alginate powders: compression force as a function of displacement.

Deformation energy of the punch and die was taken into account by conducting compression experiments using an empty die at the same compression condition. The permanent work done on powders during the compression process is defined as the difference between the work of compression (positive sign) and the work of decompression (negative sign) as shown in Equation 31:

$$W_{c/d} = W_{compression} + W_{decompression} \text{ ,} \qquad \text{Equation 31}$$

% Elasticity during compression is defined as:

$$\%\text{Elasticity} = \frac{\left|W_{decompression}\right|}{W_{compression}} \times 100\% \text{ ,} \qquad \text{Equation 32}$$

Out-of-Die Heckel Plot

The Heckel model describes the consolidation process as a first-order reaction of compact porosity with respect to the applied compaction pressure:

$$\ln\left(\frac{1}{\varepsilon}\right) = k \cdot P + A \text{ ,} \qquad \text{Equation 33}$$

where ε is porosity of compact at applied pressure P, k is the slope of the linear portion of the plot, and A is the intercept of the linear portion when P is zero.[158] The porosity of the compact was calculated based on the powder's apparent volume and its true density. The reciprocal of the k is defined as the mean yield pressure (P_y), which reflects the plasticity of the powder: the lower the P_y values, the greater the plasticity.

In this study, sodium alginate compacts were prepared under compression pressures varying from 25 to 265 MPa. The linear portion of the Heckel plot, determined by the 1st-derivative method (Appendix II), ranged from 50 to 150 MPa.

Out-of-Die Gurnham Analysis

In 1946, Gurnham and Masson introduced an equation to describe the expression of liquids from fibrous materials including cotton, wool, *etc.*[163] In their model, it was proposed that any increase in pressure, expressed as a fractional increase over the existing pressure, results in a proportionate increase in the apparent density of the mass:

$$\frac{dP}{P} = A \cdot d\rho \qquad \text{Equation 34}$$

where P is pressure, ρ is apparent density based on solid weight and total volume, and A is a constant. Integrating Equation 34 yields:

$$\rho = a \ln(P) + b \qquad \text{Equation 35}$$

where a (unit: Pa^{-1})and b (unit: g/cm^3)are constants.

Linear relationships between apparent density and ln P were obtained for both dry and wetted fibrous materials (soaked with water or oil) except in a few cases. The volume reduction of dry fibrous material (particle slipping, fragmentation, and deformation) described in Gurnham and Masson's study may be considered similar to the processes during tablet compression. Zhao *et al.*[160] first proposed the application of Gurnham model in evaluating the compression behavior of pharmaceutical powders.

Replacing apparent density with porosity in Equation 35 yields:

$$100 \cdot \varepsilon = -c \ln(P) + d, \qquad \text{Equation 36}$$

where c (unit Pa^{-1}) and d (no unit) are constants. The constant c expresses the effect of a change in pressure on compact porosity. A large value of c indicates a strong volume reduction ability of the material under compression. In other words, a larger c value relates to a more plastic material. Out-of-die data obtained in the compression pressure range from 50 to 150 MPa were used to fit Gurnham model.

Results and Discussion

Inter-grade Variability of Sodium Alginate in Compressibility

Powder Properties

The physical properties of sodium alginate powders were determined and listed in Table 15. Bulk densities of the grades 2, 3 and 4 are comparable and that of grade 5 is ~10% smaller. Tapped density decreases from grade 2 to grade 5 from 0.973 to 0.867 g/cm^3. Carr's Index of the four grades of sodium alginate ranges from 28 to 32%. Thus, the flowability of sodium alginate powders is poor, but could be improved by the use of a glidant. The true densities of the four grades of sodium alginates vary from 1.706 to 1.723, which are comparable to the values reported by Schmid and Picker-Freyer for different grades of sodium alginate.[164] Moisture contents of sodium alginates stored in RH 31-33% range from 8.13% to 11.90%. Grade 2 has the lowest moisture content, while the other three grades are similar in moisture content. Moisture usually functions as a plasticizer of amorphous polymers, lowering the glass transition temperature and increasing the plasticity of amorphous polymers.

The particle size distribution obtained using the USP sieving method is depicted in Figure 30. The majority of particles (> 90%) for the four grades of sodium alginate are below 53 μm. Grade 4 has higher percentage of particles < 38 μm than the other three grades. Plastic materials with smaller particles usually form stronger tablets when compressed to the same porosity, due to the increased inter-particular bonding areas after compression.

Table 15. Powder properties of four grades of sodium alginate (mean ± standard deviation of three replicates).

Sodium Alginate	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	True Density (g/cm^3)	Moisture Content (%)
SA Grade 2	0.678 ± 0.020	0.973 ± 0.019	30.33 ± 1.87	1.707 ± 0.015	8.13 ± 0.18
SA Grade 3	0.655± 0.006	0.933 ± 0.005	29.78 ± 0.38	1.723 ± 0.024	11.71 ± 0.25
SA Grade 4	0.649± 0.001	0.906 ± 0.006	28.34 ± 0.52	1.716 ± 0.005	11.90 ± 0.04
SA Grade 5	0.589± 0.004	0.867 ± 0.023	32.04 ± 1.98	1.706 ± 0.006	11.69 ± 0.07

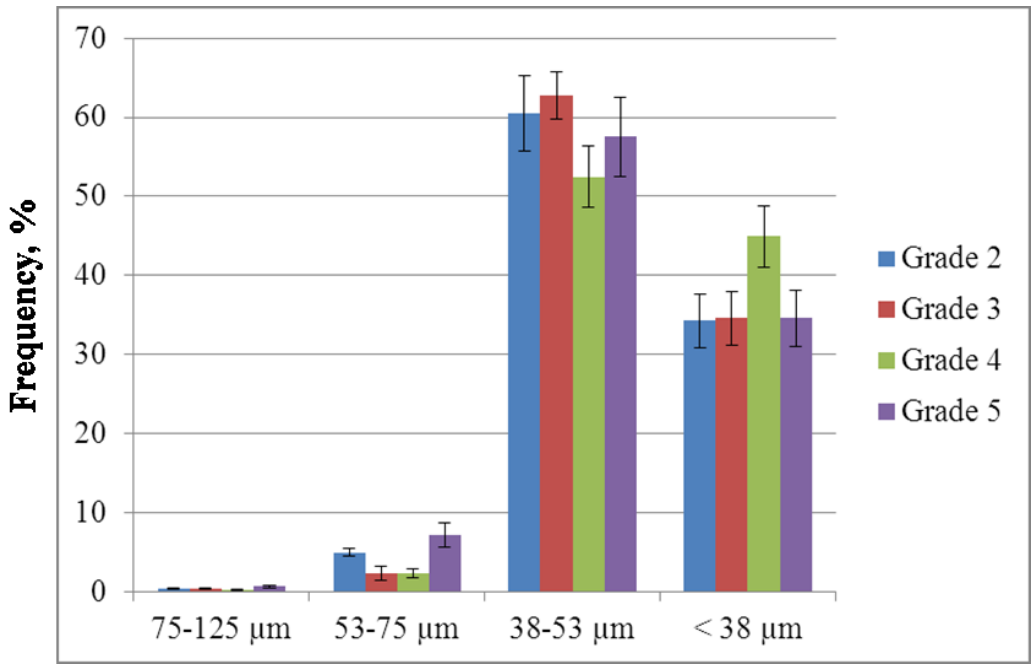

Figure 30. Particle size distribution of sodium alginate (four grades) obtained using the USP sieving method (mean ± standard deviation of three replicates).

Compressibility and Compactibility

Compression and compaction profiles of the sodium alginates, MCC PH102, and lactose anhydrous are depicted in Figure 31. The porosity of the powder bed of the alginates decreases with increasing pressure. At each compression pressure, the porosities of sodium alginate compacts are higher than that of MCC PH102 or lactose anhydrous. The tensile strength of the sodium alginate compacts increases with decreasing porosity.

Compactibility is the ability of a powder to be transformed into tablets with strength during densification. It is represented by a plot of tensile strength as a function of porosity in Figure 31(b). The compactibility of pharmaceutical powders can generally be described by the Ryshkewitch equation:[174]

$$\sigma_T = \sigma_{T,0} e^{-k\varepsilon}, \qquad \text{Equation 37}$$

where σ_T is tensile strength, $\sigma_{T,0}$ is tensile strength at zero porosity, k is a constant, and ε is porosity. The compactibility data for sodium alginates, MCC PH102, and lactose anhydrous was fit to equation 37 using nonlinear regression (GraphPad Prism, La Jolla, CA, USA). The best-fit lines are presented in Figure 31(b). As can be seen in Figure 31(b), at any fixed porosity value in the range from 0.20 to 0.25, MCC PH102 compacts have the highest tensile strength, lactose anhydrous compacts have the lowest tensile strength, and sodium alginates compacts have intermediate tensile strength. Among the four grades, compacts of grades 2, 3, and 5 are similar in tensile strength, while compacts of grade 4 are higher in tensile strength the other three grades, at any fixed porosity in the range from 0.20 to 0.25. The smaller particle size of grade 4 might contribute to the higher tensile strength of compacts prepared from grade 4 than compacts prepared from other three grades.

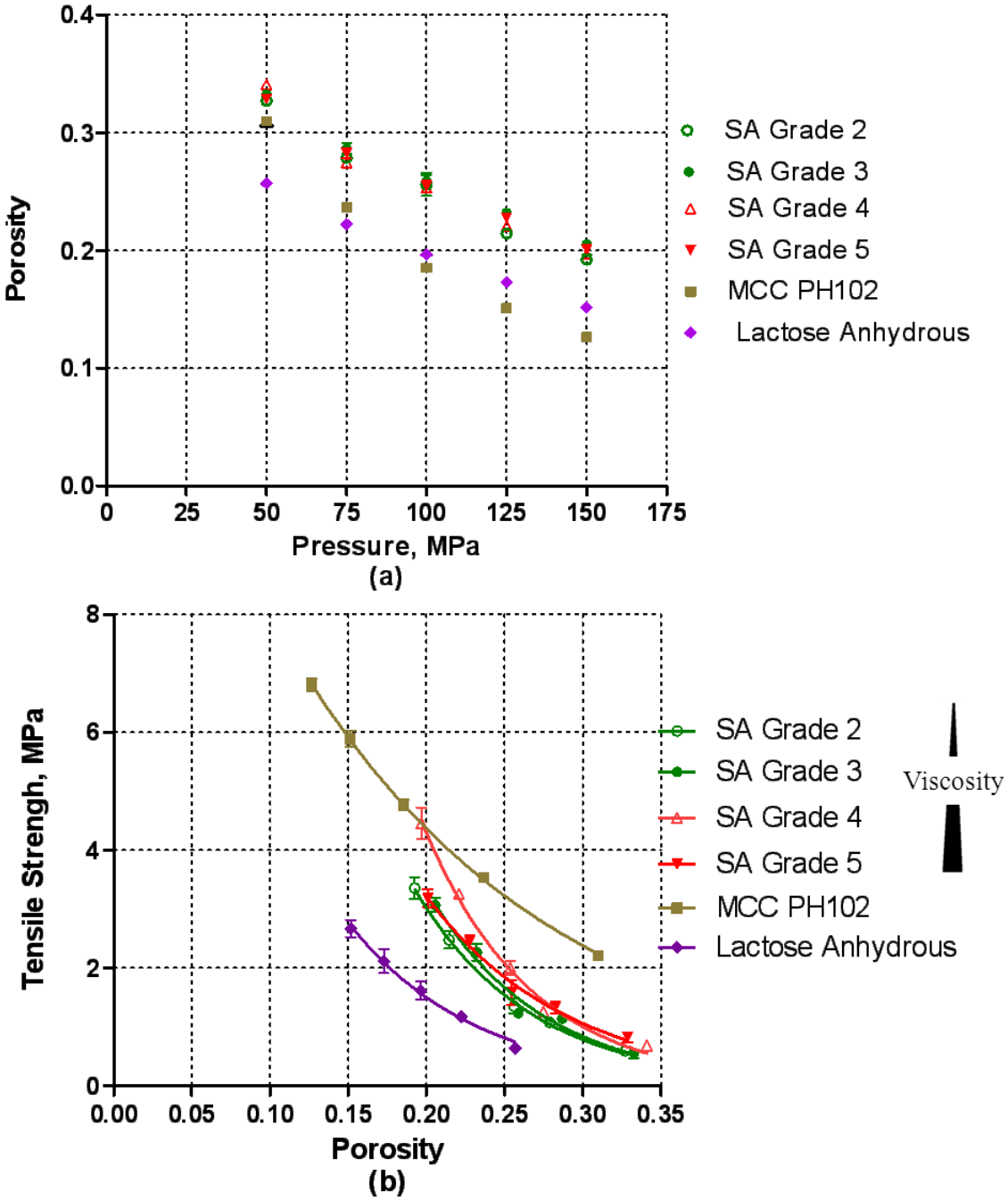

Figure 31. (a). Porosity of sodium alginate compacts as a function of compression pressure; (b). Tensile strength of compacts as a function of porosity.

Compaction Energetics

The compaction energetics, $W_{c/d}$ and $W_{decompression}$, for the four grades of sodium alginate along with MCC PH102 and lactose anhydrous, are plotted as a function of compression pressure in Figure 32. Both $W_{c/d}$ and $W_{decompression}$ values increase with increasing compression pressure for all the materials investigated. In the whole range of compression pressure investigated, MCC PH102 has the highest $W_{c/d}$, lactose anhydrous exhibits the lowest $W_{c/d}$, and sodium alginates show $W_{c/d}$ in between the two reference materials. It was reported that $W_{c/d}$ at intermediate compression pressure (127MPa) is relatively a good indicator of a material's plasticity.[170] Thus, the $W_{c/d}$ values at 125 MPa for the excipients investigated are listed in Table 16. ANOVA and the subsequent multiple pair comparisons tests revealed that only grades 2 and 3 are not significantly different in their $W_{c/d}$ values while all other pairs are significantly different in their $W_{c/d}$ values (three replicates, $p < 0.05$). Sodium alginates with higher molecular weights (grades 4 and 5) show larger $W_{c/d}$ values, although the differences are less than 7% when compared with grades at lower molecular weights (grades 2 and 3).

Lactose anhydrous demonstrates the lowest $W_{decompression}$ at every pressure level. MCC PH102 shows similar $W_{decompression}$ as sodium alginates at compression pressures ≤100 MPa. At higher compression pressures, MCC PH102 has $W_{decompression}$ close to grade 4, and lower than the other grades. Grade 4 exhibits lower value of $W_{decompression}$ than the other three grades in the whole compression range investigated.

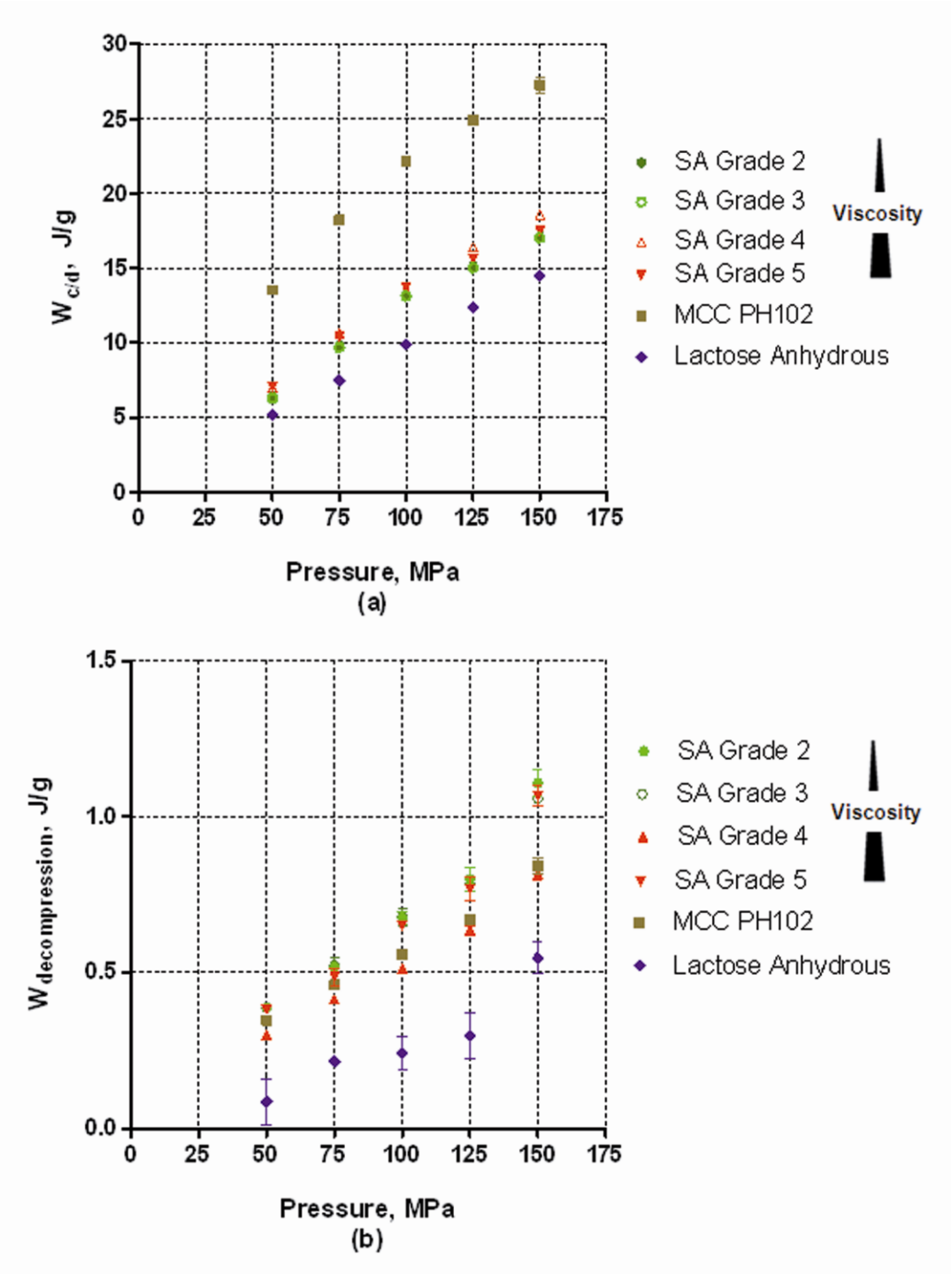

Figure 32. Compaction energetics as a function of compression pressure for the four grades of sodium alginate, MCC PH102, and lactose anhydrous: (a). $W_{c/d}$; (b). $W_{decompression}$.

The % Elasticity as a function of compression pressure is plotted in Figure 33. MCC PH102 and lactose anhydrous demonstrate similar % Elasticity in the pressure range investigated. The % Elasticity values for MCC PH102 and lactose anhydrous keep almost the same (2.4-2.8%) from 50 to 125 MPa and increase slightly to 3.0-3.6% at 150 MPa. The % Elasticity values of the four grades of sodium alginate decrease slightly (< 1%) from 50 MPa to 100 MPa, and then increase slightly (< 1%) from 100 MPa to 150 MPa. All four grades of sodium alginate demonstrate higher % Elasticity than both MCC PH102 and lactose anhydrous. Thus, it is in agreement with Schmid and Picker-Freyer's conclusion that sodium alginates deform more elastically than MCC during compression.[164]

Grade 4 shows the lowest % Elasticity among the four grades of sodium alginate. The four grades of sodium alginate show similar $W_{c/d}$ values during compression, suggesting that the energies applied for volume reduction and consolidation (bond formation among particles) are similar for the four grades. On the other hand, the elastic recovery during decompression breaks the bonds formed during compression. The higher % Elasticity would result in lower tablet strength. The lower % Elasticity of grade 4 could partly explain the higher tensile strength of the compacts of grade 4 than the compacts of other grades when compressed to the same porosity. The lower % Elasticity of grade 4 might be due to the fact that grade 4 has a relatively higher portion of small particles than other grades. When compressed to the same porosity, small particles are usually associated with larger bonding areas, forming stronger inter-particular interactions and eventually stronger compacts than larger particles.

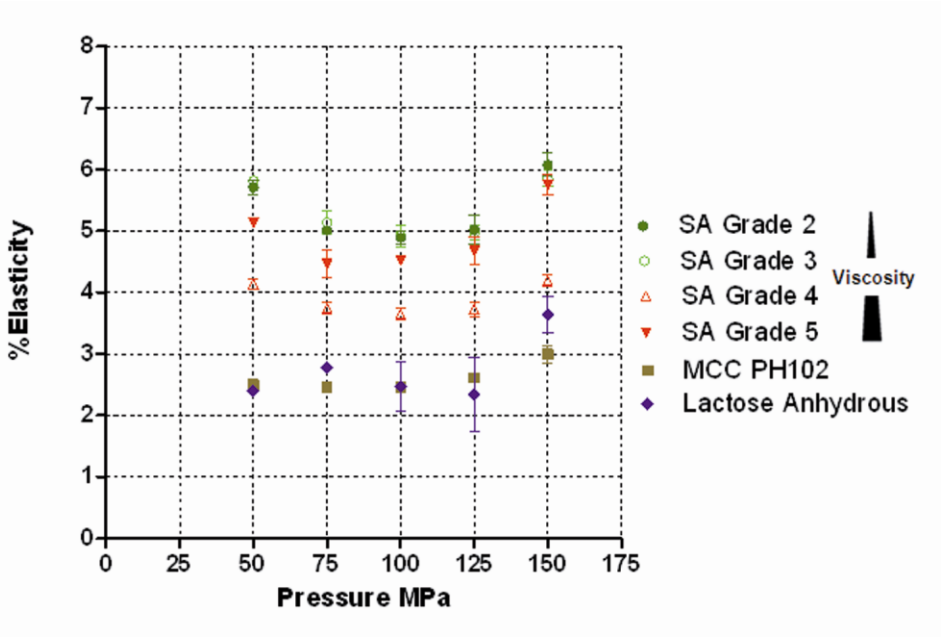

Figure 33. The % Elasticity as a function of compression pressure for sodium alginates, MCC PH102, and lactose anhydrous.

Out-of-Die Heckel Analysis

Linear regression of the "out-of-die" Heckel plots for all excipients was performed in the compression pressure ranging from 50 to 150 MPa (Figure 34), and a summary of the mean yield pressure (P_y) values and R^2 values is listed in Table 16. MCC PH102 shows the lowest P_y values. The 95% confidence intervals of the four grades of sodium alginate and lactose anhydrous are similar to each other.

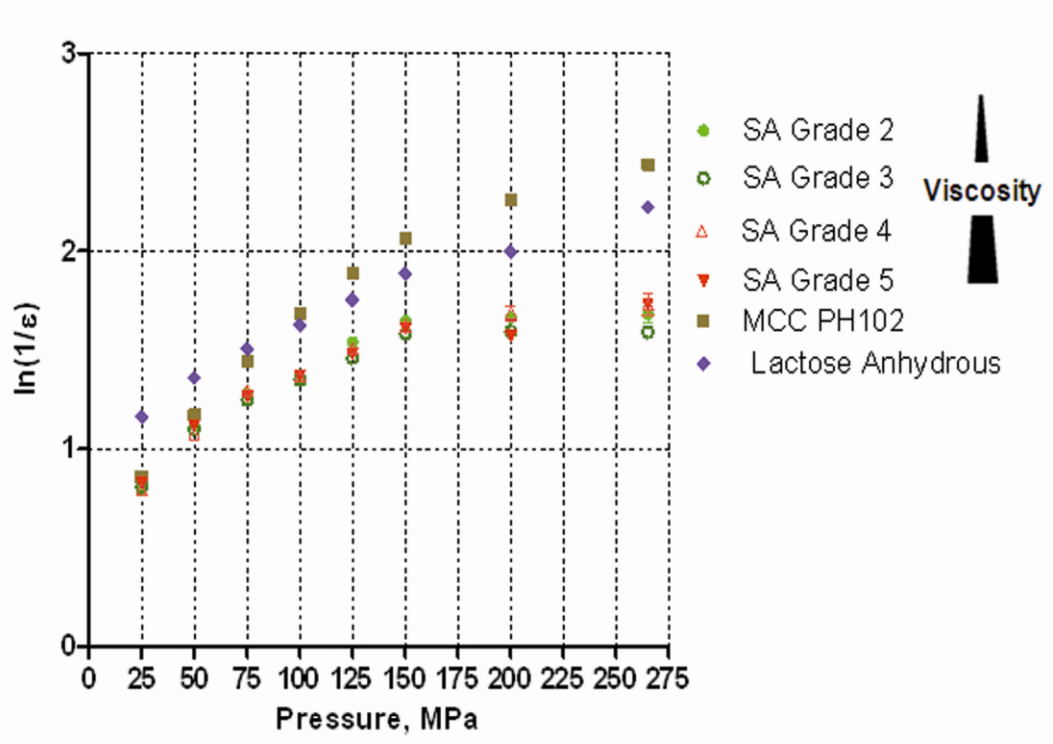

Figure 34. The out-of-die Heckel plot for sodium alginates, MCC PH102, and lactose anhydrous (data are plotted as mean and standard deviation of three replicates).

Gurnham Analysis

The compact porosity (ε) as a function of ln(P) was plotted for all excipients, and the data was analyzed by Gurnham equation via linear regression (Figure 35). The *c* values and R^2 values for Gurnham analysis can be seen in Table 16. MCC PH102 has the highest *c* values, while lactose anhydrous has the lowest *c* values. The *c* values of the four grades of sodium alginate are in between those of MCC PH102 and lactose anhydrous and closer to that of lactose anhydrous. The 95% confidence intervals of the *c* values among the four grades are overlapping each other.

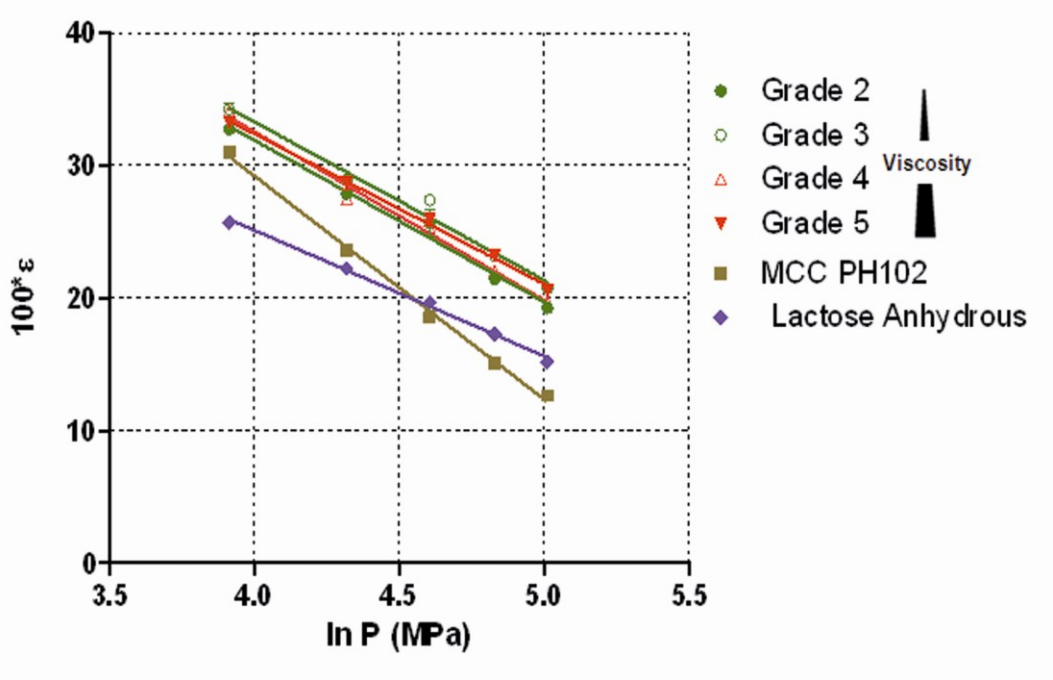

Figure 35. Gurnham analysis of compression behavior of sodium alginates, MCC PH102, and lactose anhydrous (data are plotted as mean and standard deviation of three replicates).

Table 16. A summary of the irreversible compression energy $W_{c/d}$, Gurnham *c*, Heckel P_y, and R^2 values for sodium alginates, MCC PH102, and lactose anhydrous.

Excipient	$W_{c/d}$[#] 125MPa (J/g)	Gurnham		Heckel	
		C^*	R^2	P_y* (MPa)	R^2
SA Grade 2	15.12 ± 0.05	11.12-13.24	0.9793	174.58 - 204.88	0.9833
SA Grade 3	15.02 ± 0.06	10.81-13.05	0.9761	189.00 – 223.06	0.9813
SA Grade 4	16.40 ± 0.12	11.82-13.60	0.9865	173.79 – 208.94	0.9771
SA Grade 5	15.63 ± 0.02	10.73-11.91	0.9925	202.06 – 225.07	0.9920
MCC PH102	24.90 ± 0.32	16.20-17.45	0.9961	105.88 – 118.16	0.9917
Lactose Anhydrous	12.36 ± 0.15	8.89-10.06	0.9933	184.23 – 199.96	0.9971

#: n=3; *: data reported as 95% confidence intervals.

In summary, MCC PH102 demonstrates the highest plasticity among all the materials investigated according to the results obtained by compaction energetics and the two models. It is obvious that the plasticity of sodium alginate is lower than that of MCC PH102. Based on $W_{c/d}$ and Gurnham analysis, the plasticity of sodium alginates is higher than that of lactose anhydrous. However, based on P_y values obtained from Heckel analysis, the plasticity of sodium alginates is similar to that of lactose anhydrous. Thus, the plasticity of sodium alginates is indistinguishable from that of lactose anhydrous. However, the moisture contents are different among MCC (~5% w/w), lactose anhydrous (~0.5% w/w), and sodium alginates (~10% w/w). Sodium alginates have higher moisture contents due to their amorphous nature (water penetrates into the amorphous region more

easily than the crystalline region). Sodium alginates may deform less plastically than lactose anhydrous when they have the same the moisture content.

Among the four grades of sodium alginate, there is no significant difference in compression properties between grades 2 and 3 based on compaction energetics and the two models. For grades 4 and 5, there is a statistical significance ($p < 0.05$) in their $W_{c/d}$ values (grade 4 > grade 5), although the difference is only ~5%. Thus, these four grades can be considered as similar in their plasticity during compression. Grade 2 has the lowest molecular weight and also the lowest moisture content. The same amount of sodium alginate of grade 2 has higher number of chain ends, contributing to a higher plasticity during compression due to the higher free volumes of the chain ends than those grades with higher molecular weights. On the other hand, the higher moisture contents of the other grades would contribute to a higher plasticity. Hence, the fact that grade 2 shows similar plasticity to other grades could be due to the combined effects of moisture content and molecular weight. For grades 3, 4 and 5, they have similar moisture contents. The fact that all these three grades demonstrate similar plasticity suggests that the threshold molecular weight for sodium alginate might be achieved and a further increase in molecular weight from grade 3 to grade 5 does not result in a substantial change in deformation mechanism.

However, only one batch from each grade was used in this study. The inter-batch variability within each grade was not accounted. Further studies on additional batches of each grade would provide a better understanding of the inter-grade variability of sodium alginate in compaction properties. With multiple batches from each grade included in the

further study, it might show that there are statistical significant differences in the mechanical properties of different grades of sodium alginate.

Inter-batch Variability of Sodium Alginate in Compressibility

Powder Properties

The bulk, tapped, and true density, and moisture content values for the three batches of sodium alginate (grade 3) are summarized in Table 17. Their bulk, tapped, and true density values are all respectively very close to each other. All three batches have a Carr's Index greater than 25%, which means that their flowability is poor but could be improved by the use of a glidant. The moisture contents decrease slightly from batch *A* to *J* (from 11% to 9%). Particle size distribution for the three batches is depicted in Figure 36. More than 90% w/w of the powders are below 53 μm for all three batches. Batch *G* has substantially lower percentages of particles > 53 μm than the other two batches. Batches *A* and *J* are similar in their particle size distribution.

Table 17. Powder properties of three batches of sodium alginate (grade 3) (mean ± standard deviation of three replicates).

Sodium	Bulk Density	Tapped	Carr's Index	True Density	Moisture

Alginate	(g/cm^3)	Density (g/cm^3)	(%)	(g/cm^3)	Content (% w/w)
Batch A	0.613 ± 0.004	0.826 ± 0.007	25.9 ± 1.0	1.720 ± 0.009	11.26 ± 0.10
Batch G	0.606 ± 0.007	0.876 ± 0.015	30.8 ± 1.8	1.717 ± 0.007	9.75 ± 0.10
Batch J	0.629 ± 0.012	0.874 ± 0.003	28.0 ± 1.6	1.718 ± 0.006	8.95 ± 0.36

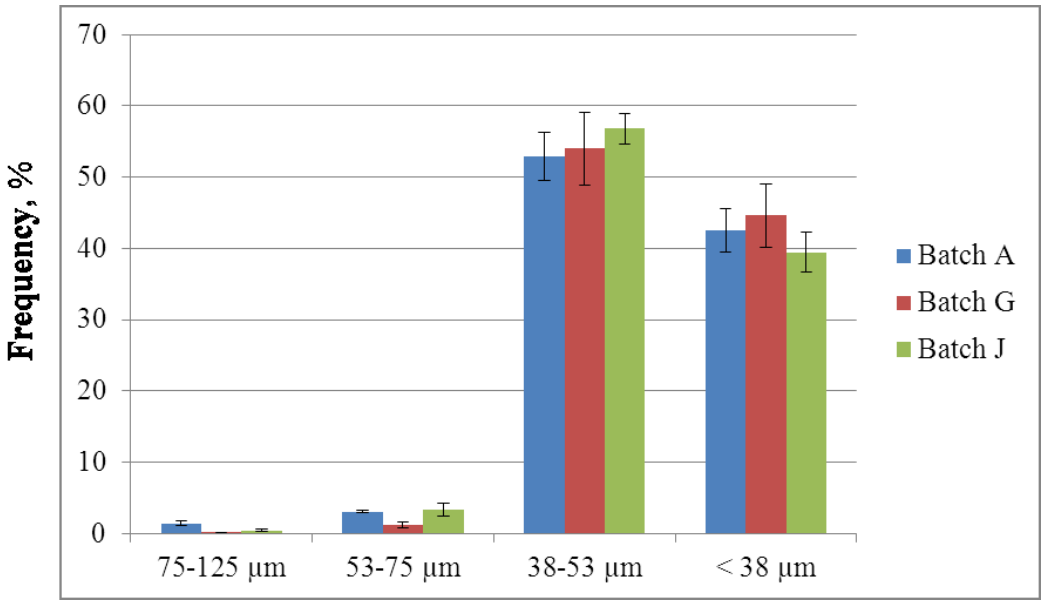

Figure 36. Particle size distribution of sodium alginate (three batches) obtained from USP sieving method (mean ± standard deviation of three replicates).

Compressibility and compatibility profiles of the three batches are depicted in Figure 37. Batch *G* shows the lowest porosity at each compression pressure. Batch *A* has relatively higher porosity than batch *J* at low pressures (50-100MPa) and has relatively lower porosity than batch *J* at high pressures (100-150MPa). Tensile strength of the sodium alginate compacts increases with decreasing porosity. The relationship between tensile strength and porosity for the three batches can be well described by the same

Ryshkewitch equation[174] with R^2 of 0.987. Thus, tensile strength of compacts prepared from the three separate batches is identical when compacted to the same porosity. This fact is important for scale-up process of sodium alginate matrix tablets. At large production scale, the compression speed is much higher than the bench-top tablet compressor. Since plastic deformation is time-dependent, higher compression speed could lead to reduced tablet strength. However, for the multiple batches of sodium alginate, the same tablet mechanical strength can be maintained in the scale-up process by adjusting parameters, such as pre-compression pressure, main compression pressure, compression speed, etc., to achieve tablets with similar porosity.

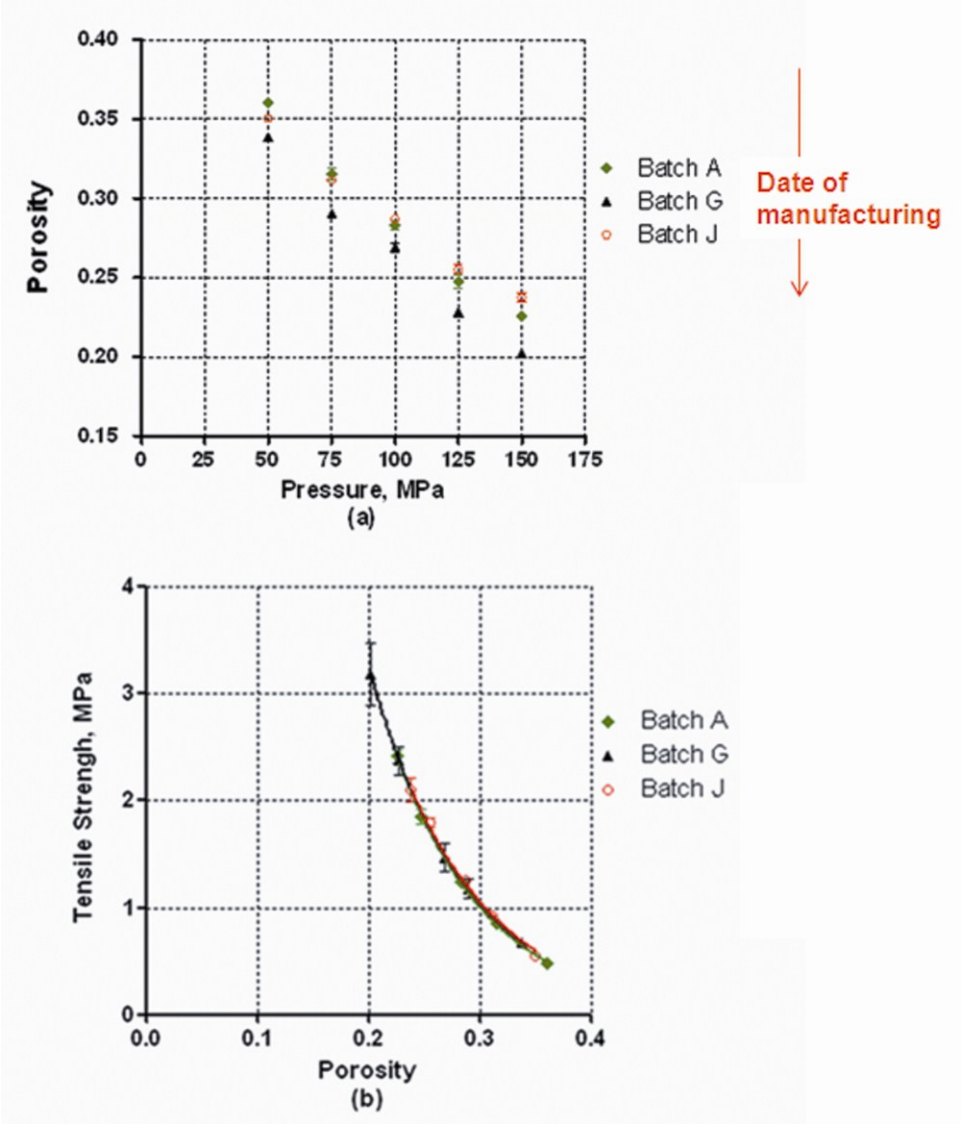

Figure 37. (a). Porosity (ε) of sodium alginate (three batches) powder under compression as a function of pressure; (b). Tensile strength of compacts (three batches) as a function of porosity. Data are reported as mean and standard deviation of three replicates.

Compaction Energetics

The compaction energetics, $W_{c/d}$ and $W_{decompression}$, and % Elasticity for the three batches of sodium alginate are plotted as a function of compression pressure in Figure 38. The three batches are similar in their $W_{c/d}$ and $W_{decompression}$ values. The $W_{c/d}$ values at 125

MPa for the three batches investigated are listed in Table 18. The % Elasticity values for the three batches are similar, varying from 4% to 6% in the pressure range investigated.

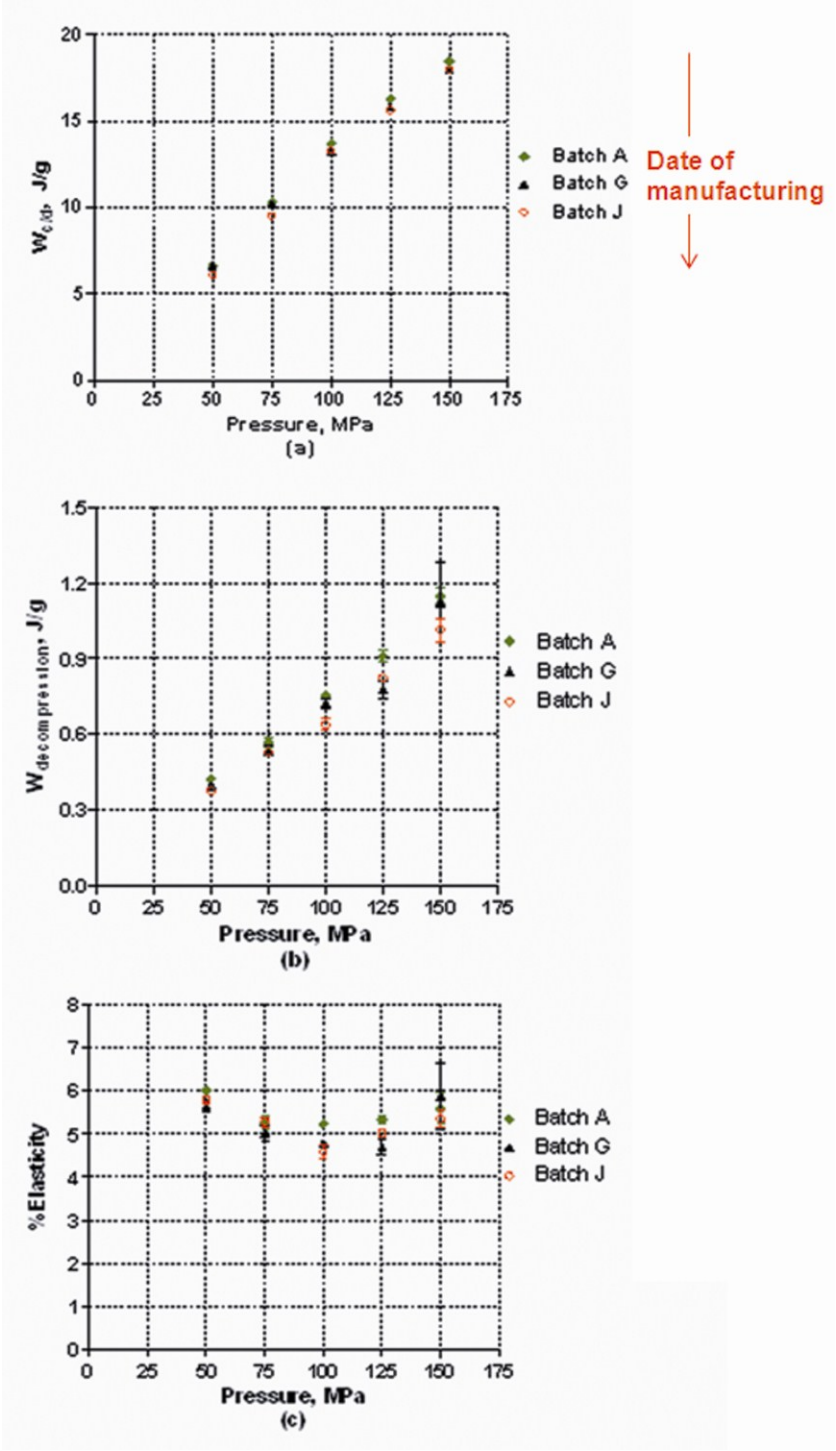

Figure 38. Compaction energetics and % Elasticity as a function of compression pressure for the three batches of sodium alginate: (a). $W_{c/d}$; (b). $W_{decompression}$;(c), % Elasticity.

Heckel and Gurnham Analysis

The out-of-die Heckel and Gurnham analysis of the compression data for the three batches are depicted in Figure 39. The results are summarized in Table 18. Batches *A* and *G* are similar in their *c* values, while batch *J* has smaller *c* values. Batch *A* shows slightly higher P_y values than batch *G*, while batch *J* exhibits the largest P_y values among the three batches.

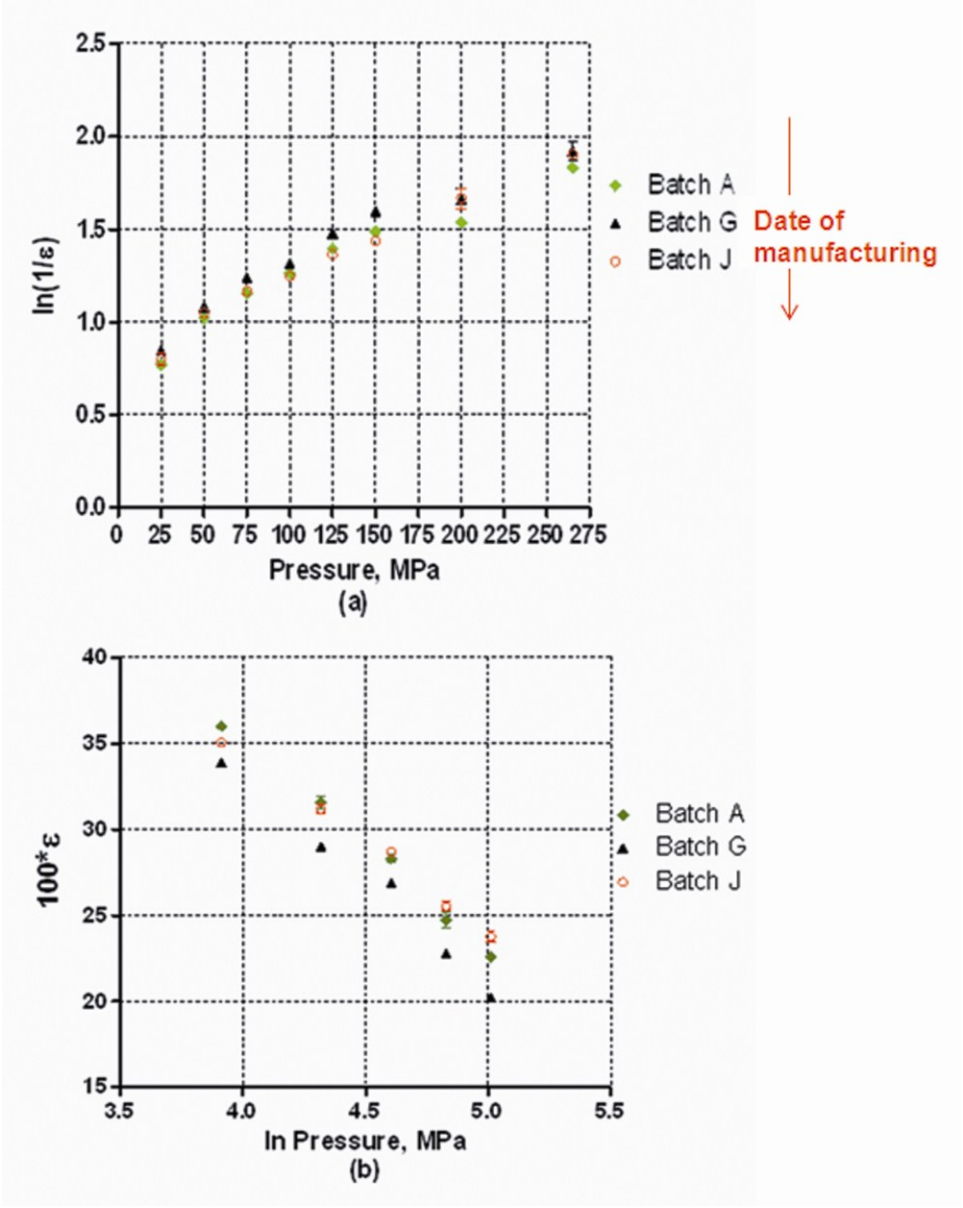

Figure 39. Out-of-die Heckel (a) and Gurnham (b) analysis of the compression data for the three batches of sodium alginate (grade 3).

Table 18. A summary of the $W_{c/d}$ at 125 MPa, Gurnham c, Heckel P_y, and R^2 values for the three batches of sodium alginates.

Excipient	$W_{c/d}$# 125MPa (J/g)	Gurnham		Heckel	
		*c**	R^2	P_y* (MPa)	R^2
Batch *A*	16.28 ± 0.02	11.68 - 12.93	0.9928	203.29 – 223.11	0.9940
Batch *G*	15.83 ± 0.07	11.24 - 13.16	0.9831	185.60 – 208.81	0.9904
Batch *J*	15.63 ± 0.10	9.75 - 10.89	0.9916	242.72 – 270.93	0.9916

#: n=3; *: data reported as 95% confidence intervals of three replicates.

In summary, the plasticity of the three batches are similar to each other based on $W_{c/d}$ values at 125 MPa (< 5% difference). Gurnham analysis indicates that Batches *A* and *G* are similar in their plasticity while batch *J* is slightly less plastic (~20% less in *c* value). Heckel analysis suggests that batches *A* and *G* are slightly more plastic than batch *J*. Based on the study on multiple grades, the molecular weight of these three batches should've exceeded the threshold value and would have minimal influence on the compression behavior of these batches. Batch *J* has the lowest moisture content, which might be one of the reasons of its lowest plasticity among the three batches. Between batch A and batch G, batch *G* has the lower molecular weight (positive contribution to plastic deformation) and lower moisture content (negative contribution to plastic deformation), which may explain the similar plasticity between these two batches.

The differences in porosity of compacts result in the differences in tensile strength of compacts prepared from these three batches at the same compression pressure: batch *G* > batch *A* > batch *J*. However, the tensile strength – porosity profiles for the three batches

indicate that the multiple batches are identical in compactibility, *i.e.*, the same tensile strength can be achieved by compressing different batches to the same compact porosity.

Conclusion

The compression behavior of various grades and batches of sodium alginate was studied by compaction energetics, the out-of-die Heckel analysis, and the out-of-die Gurnham analysis. It was found that sodium alginates deform less plastically than MCC PH102 and slightly more plastically than lactose anhydrous when stored under the same temperature and relative humidity. Sodium alginates also demonstrate more elastic deformations during compression than both MCC PH102 and lactose anhydrous. For direct compression, tablets prepared from a mixture of sodium alginate and MCC PH102 would be expected to have acceptable mechanical properties for industrial application. The four grades of sodium alginate investigated are similar in their compressibility and compatibility. However, only one batch for each grade was compared in this study. Multiple batches from each grade would provide a better view on the inter-grade variability of sodium alginate in their compression properties. Surprisingly, tablets of multiple batches of one grade exhibit substantial variation in porosity under the same compression pressure. The difference in porosity could be mainly due to the differences in particle size and plasticity among the various batches. However, multiple batches show identical compactibility. The same tensile strength can be achieved by compressing different batches to the same porosity. When using multiple batches of sodium alginate in matrix tablets, adjustments of the compression parameters may be required to achieve tablets with similar porosity and mechanical properties.

Part 2. Sodium Alginate Matrix Tablet Functionality

Hydrophilic polymer matrices have been widely applied in peroral controlled drug release systems. Polymer matrix tablets are relatively easy and economical to formulate

and manufacture.[78] Drug release from hydrophilic polymer matrices is controlled by the hydration characteristics (swelling and/or erosion) of the polymer and the physical properties of the resultant polymer gel layer formed around the matrices.[31,175-177] Water-soluble drugs are primarily released by diffusion of dissolved drug molecules through the polymer gel layer, while poorly water-soluble drugs are mainly released by erosion of the polymer layer at the interface between the polymer gel and the bulk solution.[178]

Sodium alginate, which is able to form viscous solutions when in contact with water, has been employed to produce matrices such as beads, microspheres, and matrix tablets for extended drug release.[31,74,75,179] Sodium alginate matrix tablets can be manufactured by direct compression, which is preferred industrially due to the low cost of manufacturing.[76,78]

A useful approach to understand sodium alginate's functionality in controlled release matrix tablets is to study the swelling and erosion behavior of sodium alginate matrix tablets. The influence of multiple grades of sodium alginate — varying in both molecular weight and chemical composition — on swelling and erosion behavior of alginate-based matrix tablets has been investigated by several groups. Efentakis and Buckton's study on sodium alginate matrix tablets prepared from two grades of sodium alginate (Viscosity grade: 14 Pa·s and 0.2 Pa·s of 2% solution at 25°C, respectively. Viscosity measurement method was not specified) concluded that the high viscosity grade of sodium alginate formed a more substantial gel layer and eroded at a much lower rate in water than the low viscosity grade.[31] Sriamornsak *et al*, investigated the swelling and erosion behavior of sodium alginate matrix tablets prepared from three grades of sodium alginate (Viscosity grade: 0.3 Pa·s (high %G), 0.3 Pa·s (low %G), and 0.035 Pa·s,

respectively. Viscosity was determined on 1% solution using Brookfield LV viscometer at 60 rpm with NO. 2 spindle; temperature was not specified) in both 0.1 M HCl solution and phosphate buffer (pH 6.8).[32] Their results demonstrated that the swelling and erosion behavior of these three grades of sodium alginate were not significantly different in an acidic medium, but were significantly different in phosphate buffer. Higher viscosity grades swelled to a higher degree and eroded to a lower extent than the low viscosity grade in phosphate buffer.[32] The two grades with same viscosity but different %G did not show any significantly differences in their swelling and erosion behavior.[32] Chan *et al* ,[180] also compared the swelling and erosion behavior of two grades of sodium alginate (Kinematic viscosity 3 and 108 mm^2/s, respectively. Kinematic viscosity was determined on 1% solution using suspended-level viscometer at 37°C) in both acidic and neutral media and reached the same conclusion as Sriamornsak *et al*.[32]

There are three main issues regarding the aforementioned swelling and erosion studies. First, the grades of sodium alginate used in these three studies are substantially different in their viscosities (70 times, 9 times, and 36 times different in viscosity for sodium alginates used in the three aforementioned studies, respectively). Thus, it would not be surprising to detect significant differences in the swelling and erosion behavior. Grades with similar viscosity specifications, whether produced by the same manufacturer or different manufacturers, are more likely to be considered to be interchangeable. Hence, it is necessary to investigate the swelling and erosion behavior of sodium alginate grades with similar viscosities. Furthermore, the possible differences in swelling and erosion behavior of multiple batches of the same grade of sodium alginate should be examined as well. Second, the apparent viscosity data for the various grades of sodium alginate used

in the previous studies are "one-point" viscosity data obtained at one concentration, one shear condition, and one temperature. Study of the rheological properties of sodium alginate solutions in Chapter 2 demonstrated that "one-point" viscosity data obtained by simple viscometry do not adequately reflect the rheological behavior of sodium alginate solutions at higher concentrations under different shear conditions. Inter-grade and inter-batch variability of sodium alginate is insufficiently characterized by their "one-point" apparent viscosities. Third, the previous swelling and erosion studies were conducted by exposing the whole tablet to the dissolution medium. Consequently, the changing surface area and volume of the swelling tablets during the experiment can be expected to markedly affect the apparent erosion and swelling behavior of the whole tablets.

To address these issues, four grades of sodium alginate, and three batches of one grade were selected to study the swelling and erosion behavior of sodium alginate matrix tablets. Among the four grades (grades 2, 3, 4, and 5), grades 2 and 3 are in the same viscosity range as specified by the manufacturer. Grades 4 and 5 are also in the same but relatively higher viscosity range (< 500% difference in viscosity among these different grades). For swelling and erosion experiments, a specially designed cylindrical tablet holder was employed to expose only the upper flat surface of the tablets to the dissolution medium. Weight changes due to water update and polymer dissolution were determined at various time points. Furthermore, the continuous changes of the hydrated polymer layer thickness of sodium alginate matrix tablets were determined by the texture analysis method according to the method proposed by Yang *et al*.[181] The release profile of a model drug, Acetaminophen, from sodium alginate matrix tablets was also studied.

Finally, the relationship between the rheological properties of sodium alginate solutions and the functionality of the sodium alginate matrix tablets was investigated.

Materials and Methods

Materials

Four grades (one batch each) and three batches of one grade of sodium alginate (LF120M, grade 3) were provided by FMC Biopolymer (Drammen, Norway). Physicochemical properties, previously determined for these grades and batches were listed in Table 14 in Chapter 3 Part I. Apparent viscosity of alginate solutions increases from grade 2 to grade 4. Batches *A* to *J* were named based on their manufacturing date with batch A as the earliest batch. Deionized water was obtained from a *Milli-Q* ultrapure water system (Millipore Corp., Billerica, MA, USA). Acetaminophen (USP grade) was purchased from Spectrum Chemicals (Gardena, CA, USA) and the particles < 53 μm were used in drug release studies from sodium alginate matrix tablets.

Methods

Rheological Measurements of Sodium Alginate Solutions

The procedures employed in generating the steady shear and small amplitude oscillatory data for the sodium alginate solutions were described in the materials and methods section in **Chapter 2**.

Preparation of Sodium Alginate Matrix Tablets

Sodium alginate matrix tablets were prepared by direct compression using an Instron Universal Testing Machine (model 5869) equipped with a 50 kN load cell (Instron, Norwood, MA, USA). Sodium alginate powders (400 ± 1 mg) were filled into a 12-mm die (Carver, Inc., Wabash, IN, USA) and were compressed using flat-faced punches (Carver, Inc., Wabash, IN, USA) at 10 mm/min to 30 kN (*i.e.,* 265 MPa), held for 10 seconds, and decompressed at 10 mm/min. All powders and compacts were stored at room temperature (typically 20–22ºC) and controlled humidity (31-33% relative humidity) which was achieved by saturated $MaCl_2$ solution.[171]

Porosity of Matrix Tablets and Tensile Strength

The procedures employed in generating porosity and tensile strength data for the sodium alginate compacts were described in the materials and methods section in **Chapter 3 Part 1**.

Water uptake

A specially designed tablet holder, *i.e.*, a cylindrical polyacetal block (diameter: ~15 mm; height: ~15 mm) with a hole in the middle (diameter: ~12 mm; depth: ~12 mm), was used in the swelling and erosion studies (Figure 40).

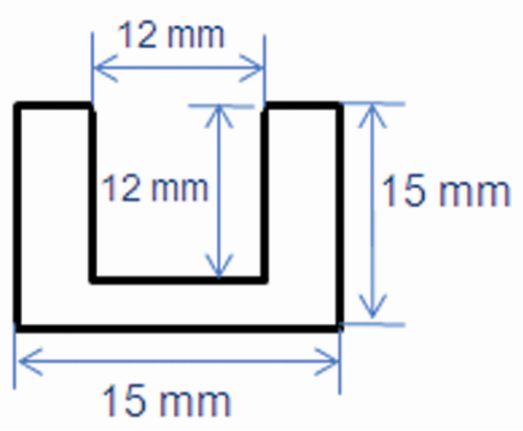

Figure 40. Schematic illustration of the tablet holder.

Vacuum grease (Dow Corning Corporation, Midland, MI, USA) was carefully applied to the bottom flat surface and the side of the cylindrical alginate compacts before placing the compacts into the tablet holder. Only the upper flat surfaces of the sodium alginate tablets were exposed to the dissolution medium, *i.e.*, deionized water. Swelling and erosion studies were performed in a USP type II dissolution apparatus (Vanderkamp®600, Vankel, Palo Alto, CA, USA) with paddles stirring at 50 rpm. Weighed tablets (W_0) were placed in the tablet holder (weight, W_h) and immersed into 900 mL deionized water at 37 ± 0.5 °C. Tablet holder was placed in the center of the vessel bottom. At predetermined time points, 0.5, 1, 2, 3, 4, 5, 6, 7, 10 and 15 h, each tablet holder was withdrawn from the medium and blotted to remove excess water and weighed (W_t) on an analytical balance (Mettler Toledo, Columbus, OH, USA). The increase in total weight due to water penetration into the matrix tablets and polymer dissolution was determined for each time point according to the following equation:

$$\%\,\text{Increase-in-Total-Weight} = \frac{W_t - W_0 - W_h}{W_0} \times 100\%, \qquad \text{Equation 38}$$

Erosion

The swollen matrix tablets collected at each time point were then dried in a vacuum oven (Isotemp® Model 280A, Fisher Scientific, Pittsburgh, PA, USA) at 85°C for at least 24 h, cooled in a desiccator, and weighed until constant weight ($W_{t,\,dry}$) was achieved. Three matrix tablets were used for each time point. Three intact tablets were dried, cooled, and weighed to determine the average dried weight ($W_{0,\,dry}$) of the initial matrix tablets. The remaining weight percentage of tablets after polymer dissolution was estimated for each time point according to the following equation:

$$\%\,\text{Polymer-Remaining} = \frac{W_{t,dry}}{W_{0,dry}} \times 100\%, \qquad \text{Equation 39}$$

Hydrated Polymer Layer Thickness

The movement of water penetration front and the dynamics of hydrated polymer layer formation as a function of time were evaluated by texture profiling analysis method modified from a previous report.[181] The test was done on an Instron Universal Testing Machine (model 5869) equipped with a 50 N load cell (Instron, Norwood, MA, USA). A cylindrical probe (2mm in diameter) attached to the load cell travels at constant speed (10 mm/min) into the swollen tablets inside the tablet holder while the force of resistance encountered by the probe and the distance traveled by the probe during the test were measured. The measurement starts at a trigger force (0.01 N) to indicate the swollen gel surface (the solution-gel interface or the erosion front) and it stops at a predetermined

stop force chosen to distinguish between the hydrated polymer layer and the remaining solid core of the tablet (the swelling front). The stop force was based on measurements on dry tablets, for which the recorded force-displacement curve was very steep: the gradient of the curve was larger than 150 N/mm. The force-displacement curves for the dry tablets and the partially-swollen tablets were comparable for forces above 15 N. Thus, the stop force was set to be 15 N. An initial indentation of 100 μm on dry tablets was recorded under 15 N load. Thus, 100 μm was deducted from the displacement between trigger force and stop force for the calculation of hydrated polymer layer thickness.

Drug Dissolution

Acetaminophen and sodium alginate (1:9 w/w) powder (4 grams in total) was mixed on Thinky Mixer (Model ARM 310, Thinky USA, Laguna Hills, CA, USA) at 2000 rpm for 1 min. Blending endpoint was determined when relative standard deviation (%RSD) of acetaminophen content in samples taken from three different locations in the mixing container was < 5%. Acetaminophen (40 mg)-sodium alginate (360 mg) matrix tablets were prepared using flat-faced punches (12 mm in diameter, Carver, Inc., Wabash, IN, USA) at 10 mm/min to 30 kN (*i.e.*, 265 MPa), held for 10 s, and decompressed at 10 mm/min. Tablets were placed inside the same tablet holders as described in the *Water uptake*.

Drug dissolution test was performed on a VanKel® Dissolution Apparatus (Palo Alto, CA, USA) using USP Apparatus II with paddle rotation speed at 50 rpm. The dissolution medium was 900 mL of deionized water with temperature maintained at 37 ±

0.5°C. At predetermined time points, 5 mL of samples were collected from the dissolution medium followed by addition of an equal volume of preheated deionized water. Acetaminophen concentrations of the samples were determined by calculation based on UV absorption at 244 nm on a Cary 3 UV/Vis Spectrometer (Varian/Agilent technologies, Santa Clara, CA, USA) according to a standard curve generated from 0.1 to 50 μg/mL ($R^2 = 0.9999$). Three samples were tested for each time point.

Data Analysis

The obtained data for the different grades and batches were analyzed via analysis of variance (ANOVA) and Levene's test for homogeneity of variance using PASW Statistics 18 for Windows (SPSS Inc., Chicago, USA). *Post hoc* testing ($p < 0.05$) of the multiple comparisons was performed by either the Tukey HSD (Honestly Significant Difference) test or Games–Howell test depending on whether Levene's test was insignificant or significant, respectively. GraphPad Prism (version 5, GraphPad Software, Inc., La Jolla, CA, USA) was used for the linear and nonlinear regression analysis of the data where appropriate.

Results and Discussion

Inter-Grade Variability

Porosity of the sodium alginate matrix tablets prepared from four different grades varied from 0.17 to 0.19 as shown in Table 19. The tensile strength of sodium alginate

tablets, ranging from 5.13 to 5.85 MPa, was not observed to be significantly different among the four grades.

Table 19. Matrix tablet porosity and tensile strength for the four grades of sodium alginate.

Sodium Alginate	Porosity[a]	σ_T[a] (MPa)
Grade 2	0.18 ± 0.008	5.63 ± 0.24
Grade 3	0.19 ± 0.007	5.26 ± 0.36
Grade 4	0.17 ± 0.006	5.85 ± 0.63
Grade 5	0.17 ± 0.003	5.13 ± 0.25

[a] n=3.

Water uptake and erosion

Sodium alginate tablets exposed to water undergo swelling with the formation of a gel layer. The water uptake and erosion behavior of matrix tablets prepared from four grades of sodium alginate are depicted, as a function of time, in Figure 41. For all four grades, the tablet weight continues to increase during the first 4 h as water penetrates into the matrix. Grades 2 and 3 show a drop in the % Increase-in-total-weight from 7 h to 15 h while the swollen tablet weight for grades 4 and 5 remains relatively constant over the duration of the experiment. Previous studies of the swelling behavior of sodium alginate matrix tablets showed similar water uptake profiles: water uptake increased at the

beginning and remained approximately constant for high viscosity grades of sodium alginate but decreased for low viscosity grades at longer times.[31,32]

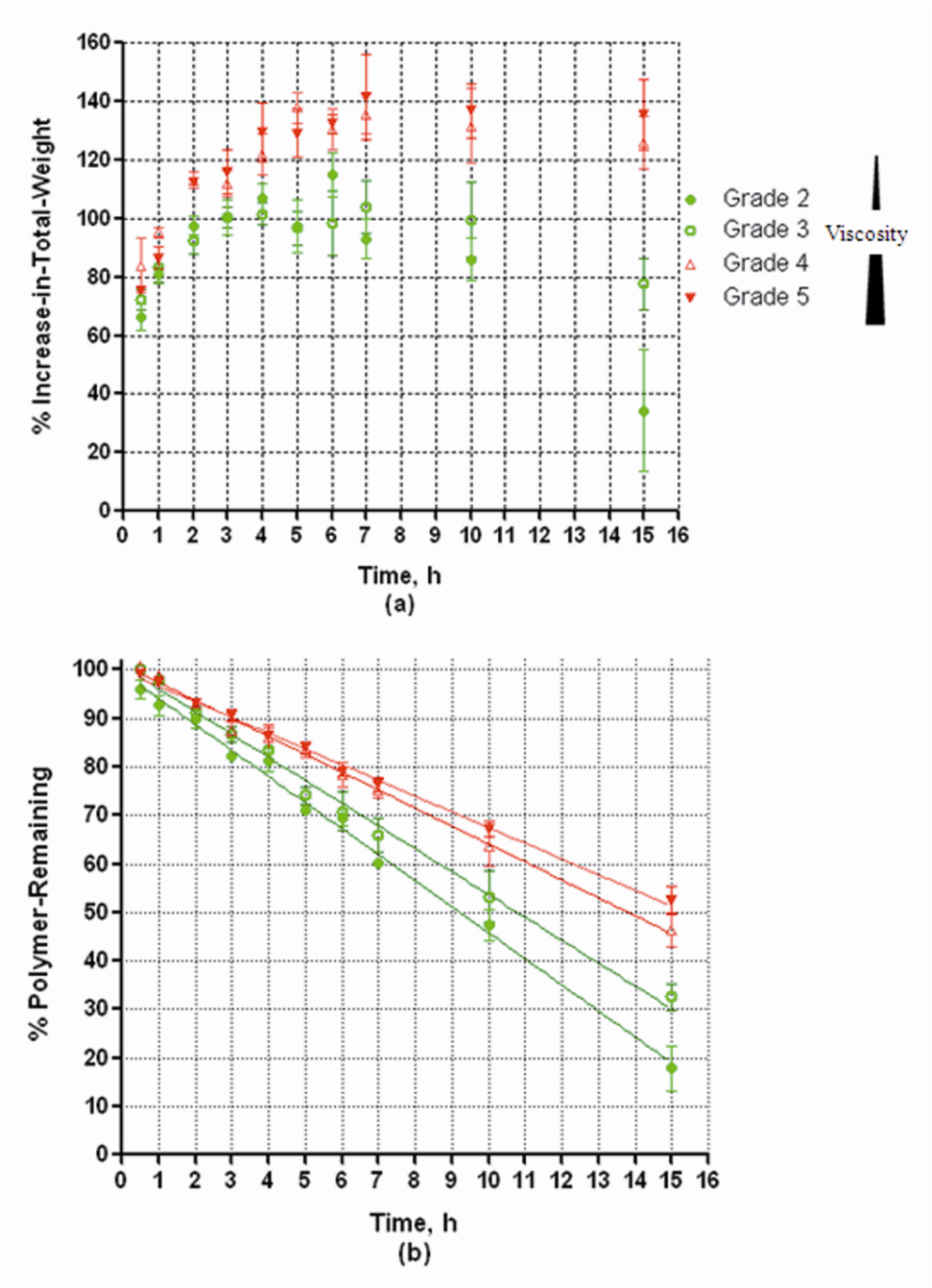

Figure 41. Swelling and erosion behavior of sodium alginate matrix tablets: (a) the percentage of increase-in-total-weight; (b) percentage of polymer-remaining. Data are shown as the mean and standard deviation of three replicates.

The four grades of sodium alginate are comparable in their % Increase-in-total-weight values in the first four hours. Grades 4 and 5 have a similar % Increase-in-total-weight profile over the whole time range investigated. Grades 2 and 3 demonstrate a significantly ($P < 0.05$) smaller % Increase-in-total-weight than grades 4 and 5 after 5 h. The % Increase-in-total-weight of grade 3 is not significantly different from that of grade 2 during the first 10 h and becomes significantly higher than grade 2 at 15 h.

Grades 4 and 5 are not significantly different in their % Polymer-remaining in the time range investigated, while grades 2 and 3 show significantly faster erosion rate than grades 4 and 5 as reflected in their smaller values of % Polymer-remaining after 5 hrs. Grade 3 has similar % Polymer-remaining to grade 2 in first 10 h and becomes significantly higher than grade 2 at 15 h. The significant differences observed among grades for water uptake behavior after 5 h could be attributed to the significant differences in erosion behavior.

The process of erosion or polymer dissolution under defined fluid dynamics conditions from a swollen polymer gel layer has been envisioned as polymer disentanglement from the polymer gel followed by polymer diffusion through the diffusion layer to the bulk solution.[182,183] The polymer dissolution process can be described by the following equation: [170]

$$m_p = m_0 - \left(k \cdot A \cdot C_d \cdot t\right), \qquad \text{Equation 40}$$

where m_p is the remaining polymer weight at time t, m_0 is the dry tablet weight at $t = 0$, k is a constant dependent on the average diffusion coefficient (D_{ave}) of the polymer in the diffusion layer, A is the surface area of the swelling tablet exposed to the dissolution medium, and C_d is the disentanglement or critical concentration at which polymer chains start to disentangle from the polymer gel under the influence of external shear. The C_d values correspond to polymer solutions with a certain threshold viscosity/viscoelasticity high enough to resist the external shear.[118,183,184] Under the same shear conditions, the C_d values of the matrix tablets prepared from the various grades of sodium alginate are a function, in part, of the rheological properties of the polymer solutions and would be constant during the polymer erosion process.[183] The erosion data of the four grades of sodium alginate as shown in Figure 41b were fitted to equation 40 by linear regression; the slopes and R^2 values are listed in Table 20. All four grades show good fit with $R^2 >$ 0.98. Slopes, representing the polymer dissolution rate, differ among the four grades with the following rank order: grade 2 > grade 3 > grade 4 > grade 5.

Table 20. Slope and R^2 values of the linear regression fit for the erosion profile of the four grades of sodium alginate.

Sodium Alginate	Slope*	R^2
Grade 2	-5.37 ± 0.12	0.9873
Grade 3	- 4.71 ± -0.13	0.9805
Grade 4	- 3.70 ± 0.09	0.9823
Grade 5	- 3.24 ± 0.07	0.9881

* n=3.

The differences in erosion behavior of the four grades of sodium alginate matrix tablets could be partly explained by their rheological behavior in solution. The erosion rate of sodium alginate matrix tablets is determined by the average diffusion coefficient (D_{ave}) and critical concentration (C_d). According to the Stokes-Einstein equation:

$$D = \frac{kT}{6\pi\eta r}, \qquad \text{Equation 2}$$

the polymer diffusion coefficient is inversely proportional to the apparent viscosity of the polymer solutions in the diffusion layer. Grades 2 and 3 have similar critical concentrations (C_d) to grade 4 but lower apparent viscosities in the diffusion layer than grade 4. It is very likely that the lower apparent viscosities of solutions of grades 2 and 3 in the diffusion layer lead to a larger D_{ave} of polymer in the diffusion layer and hence faster erosion rates for grades 2 and 3. Although grade 5 has a higher critical concentration than the other grades, it has higher apparent viscosities in the diffusion layer than the other grades. It appears that the high apparent viscosities of grade 5 at low concentrations (1-3% w/w) substantially influence the erosion process, resulting in an erosion rate slower than the other grades. Therefore, the rheological properties of sodium alginate at both low and high concentrations could be important parameters for predicting the swelling and erosion behavior of sodium alginate in matrix tablets. Grades with higher apparent viscosities at low solution concentrations and higher viscoelasticity at high solution concentrations (lower C_d) tend to form matrix tablets with slower rates of erosion and higher rates of swelling.

Hydrated polymer layer dynamics

A representative force-displacement profile for the swelling sodium alginate tablets at different time points is depicted in Figure 42 (Details for four grades and three batches of sodium alginate are listed in APPENDIX II). Based on the force-displacement profile, a typical schematic is created to illustrate the changing phases due to water penetration into the polymer matrix (Figure 43). An overall increase in hydrated polymer layer of sodium alginate tablets is observed with respect to swelling time. The hydrated polymer layer thickness as a function of swelling time for the four grades of sodium alginate is illustrated in Figure 44. The hydrated polymer layer thickness for all four grades is similar to each other at 1 h. At 5 h, the hydrated polymer layer becomes thicker for all four grades. Grades 4 and 5 have the similar hydrated layer thickness. Grades 2 and 3 also show similar thickness, which is much lower than grade 4 or 5. At 10 h, the hydrated layer thickness for all four grades is similar to the thickness at 5 h. At 15 h, the hydrated layer thickness increases slightly for grades 3, 4, and 5. Grade 2's hydrated layer remains similar thickness from 5 h to 15 h. At 15 h, Grades 4 and 5 are still similar in their hydrated layer thickness and Grade 3 has slightly higher hydrated layer thickness than grade 2.

The hydrated polymer layer thickness profile for sodium alginate tablets is similar to the water uptake profile as shown in Figure 41. At the first four or five hours, hydrated layer thickness increases with increasing water uptake into the matrix tablets. After five hours, the hydrated layer thickness keeps relatively constant for grades 4 and 5 while the weights of the hydrated tablets do not change. The hydrated layer thickness for grades 4 and 5 is larger than that of grades 2 and 3, which is in accordance with the higher amount of water uptake by tablets prepared from grades 4 and 5. For grades 2 and 3, although the

weight of swollen tablets starts to decrease after 7 hours, the hydrated layer thickness does not seem to drop simultaneously. At 15 hour, the slight increase in hydrated layer thickness could be due to the heterogeneous swelling effect of the sodium alginate particles when water front reaches the bottom of the tablets.

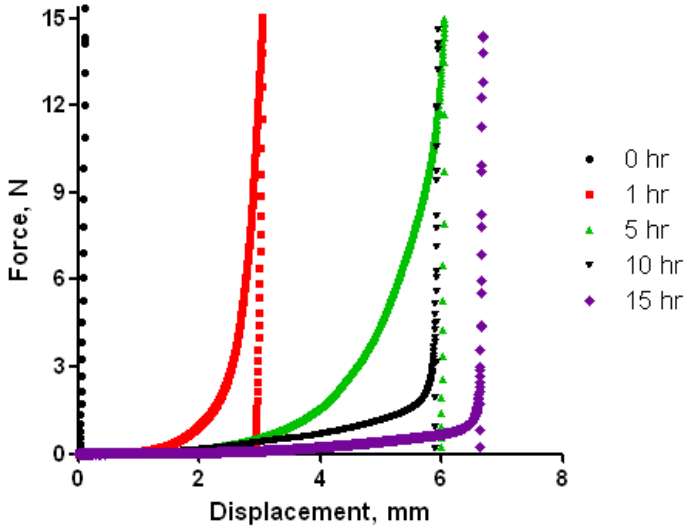

Figure 42. A typical force-displacement profile for swelling sodium alginate matrix tablets.

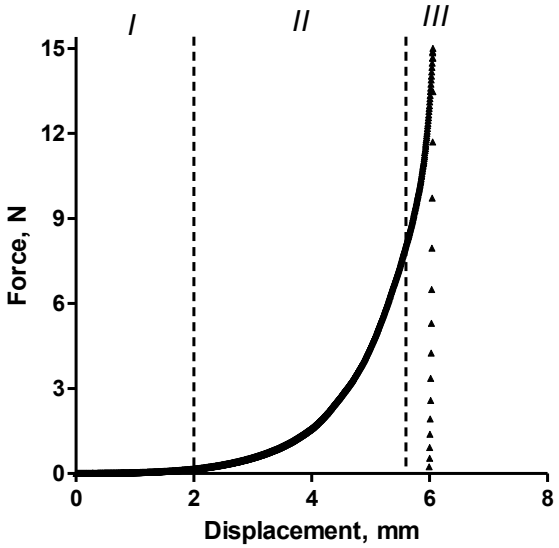

Figure 43. A schematic illustration of different regions in the polymer matrix due to water penetration: I. swollen gel layer; II. Hydrated but not swollen region; III. Dry core.

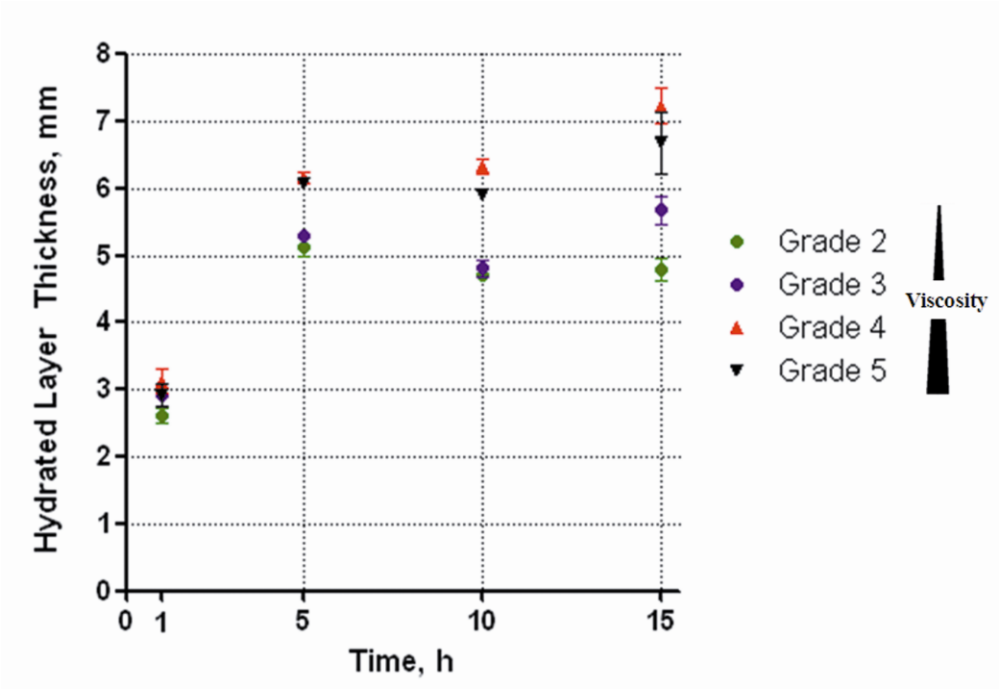

Figure 44. Hydrated polymer layer thickness as a function of swelling time for matrix tablets of four grades of sodium alginate after exposed to water.

Drug Release Studies

The porosity of Acetaminophen (APAP)-sodium alginate matrix tablets prepared from four different grades is listed in Table 21. Tablets from all four grades have similar porosities.

Table 21. Porosity of APAP-sodium alginate matrix tablets prepared from four different grades.

APAP-Sodium Alginate Tablet	Porosity
Grade 2	0.14 ± 0.003
Grade 3	0.15 ± 0.004
Grade 4	0.14 ± 0.002
Grade 5	0.15 ± 0.005

Dissolution profile of APAP from sodium alginate matrix tablets is depicted in Figure 45. Tablets prepared from grades 2 and 3 show similar APAP release profile ($P > 0.05$ at each time point). Tablets prepared from grades 4 and 5 also demonstrate similar APAP release profile ($P > 0.05$ at each time point). APAP release from tablets prepared from grades 4 and 5 is significantly slower than that from tablets prepared from grades 2 and 3 ($P < 0.01$) after four hours. The APAP release data from sodium alginate matrix tablets in this study can be well described by the zero-order equation,

$$\frac{M_t}{M_\infty} = kt \qquad \text{Equation 41}$$

,

with $R^2 > 0.97$ (the constants and R^2 are listed in Table 22). Grades 2 and 3 are similar in their *k* values; so are grades 4 and 5. The *k* values of grades 4 and 5 are smaller than those of grades 2 and 3.

The differences among the four grades in their dissolution behavior could be partly explained by their solution rheological properties. Drug release from sodium alginate matrix tablets is expected to be influenced by both sodium alginate gel erosion rate and the viscosity of sodium alginate solutions in the diffusion layer. Grades 4 and 5 demonstrate much higher apparent viscosity values (> 3 times) than grades 2 and 3 at low concentrations from 1 to 3% w/w. Since grade 4 has similar viscoelasticity with grades 2 and 3 at high concentrations, it is very likely that the substantial differences in apparent viscosity at low concentrations contribute to the slower drug release from matrix tablets prepared from grade 4 than matrix tablets prepared from grades 2 and 3. Although grade 5 shows slightly lower viscoelasticity than other grades at high concentrations, it has substantial higher apparent viscosity than grades 2 and 3 at low concentrations. This result suggests that the substantial differences in apparent viscosity at low concentrations could be the main factors determining sodium alginate's functionality in matrix tablets. On the other hand, despite the fact that grades 2 and 3 (or grades 4 and 5) do exhibit significant differences in their apparent viscosities at lower concentration according to the studies in Chapter 2, the absolute differences between these two grades in apparent viscosities are usually within 50%. This result indicates that grades with < 50% difference in their apparent viscosities at low concentrations may not show any substantial differences in their performance in matrix tablets.

Additionally, sodium alginate matrix tablets prepared from grades 4 and 5 demonstrate a thicker hydrated polymer layer than those tablets prepared from grades 2 and 3. A thicker polymer layer would decrease the amount of drug released by diffusion through the hydrated polymer layer.

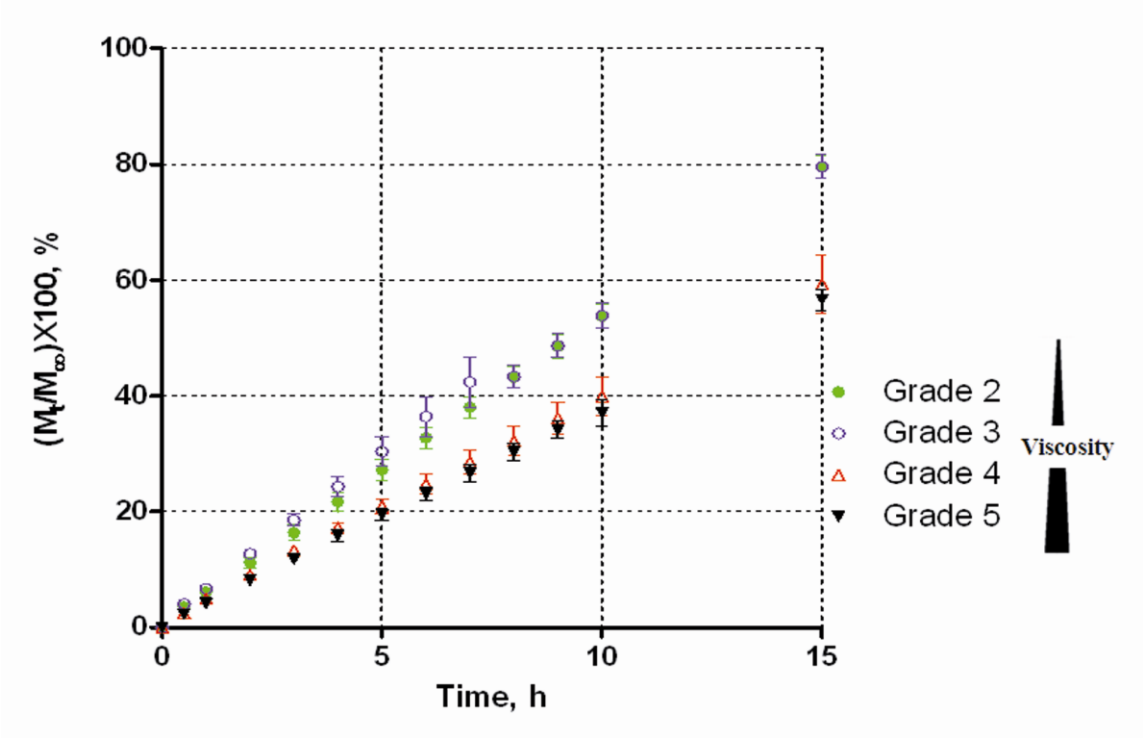

Figure 45. Acetaminophen release profile from sodium alginate matrix tablets prepared from four different grades.

Table 22. The constant, *k* (reported as mean ± standard deviation, based on three replicates), and coefficient of determination (R^2) of the linear regression fitting of the zero-order drug release data from sodium alginate (four grades) matrix tablets.

Sodium Alginate	***k***	***R*²**
Grade 2	5.41 ± 0.04	0.993

Grade 3	5.65 ± 0.08	0.973
Grade 4	4.07 ± 0.05	0.981
Grade 5	3.80 ± 0.03	0.990

Inter-Batch Variability

Porosity of the pure sodium alginate matrix tablets prepared from batches *G* and *J* is almost the same (0.16), while the porosity of batch *A* tablets is slightly higher (0.21) (Table 23). Batch *A* shows higher degree of elastic recovery than the other two batches. Tensile strength of sodium alginate tablets ranges from 4.63 to 6.21 MPa. There is no direct correlation between porosity and the tensile strength. The differences in tensile strength could be due to different plasticity and particle size among these three batches. As shown in Chapter 3 Part 1, Batch *A* and *G* are similar in plasticity, while batch *J* is relatively lower in plasticity. When compressed to the same porosity, batch *G* would have more inter-particular areas to form bonds than batch *J*. As a result, batch *G* has a higher tensile strength than batch *J*. Although batch *A* has a higher porosity than batch *J*, batch *A* may have larger bond-forming surfaces than batch *J* due to the higher plasticity of batch *A*.

Table 23. True density, matrix tablet porosity and tensile strength for the three batches of sodium alginate.

Sodium Alginate	**Porosity[a]**	**σ_T[a] (MPa)**
Batch A	0.21 ± 0.001	5.26 ± 0.23
Batch G	0.16 ± 0.002	6.21± 0.14

Batch J	0.16 ± 0.008	4.63 ±0.46

a: n=3.

The water uptake and erosion behavior of matrix tablets prepared from the three batches of grade 3 is depicted in Figure 46. All three batches show increasing water uptake during the first four hours. The swelling matrix of batch *A* has a relative constant weight from 4 h to 15 h, while batches *G* and *J* show a substantial drop in % Increase-in-total-weight from 7 h to 15 h. Batches *A* and *G* exhibit similar water uptake behavior in the first 5 h with % Increase-in-total-weight slightly but not significantly higher than that of batch *J*. After 6 h, the differences in % Increase-in-total-weight among the three batches become more substantial, with the batch rank order $A > G > J$. Batch *A* is significantly ($P < 0.05$) higher in % Increase-in-total-weight than batches *G* and *J* after 10 h, while batch *G* becomes significantly ($P < 0.05$) higher in % Increase-in-total-weight than batch *J* at 15 h. This phenomenon could be explained by the differences in the erosion behavior of the three batches as shown in Figure 46b. All three batches show similar % Polymer remaining at the first 7 hours. After 10 hours, the rank order of % Polymer remaining for the three batches are as follows: batch $A > G > J$. The % Polymer-remaining as a function of time data for the three batches of sodium alginate (as shown in Figure 46b) were fitted to equation 40 by linear regression. The slopes and R^2 values are listed in Table 24. The slopes of the equations for the three batches differ from one another with the rank order of Batch *J* > Batch *G* > Batch *A*. Batches with slower polymer erosion/dissolution rate also show higher weight gain in deionized water.

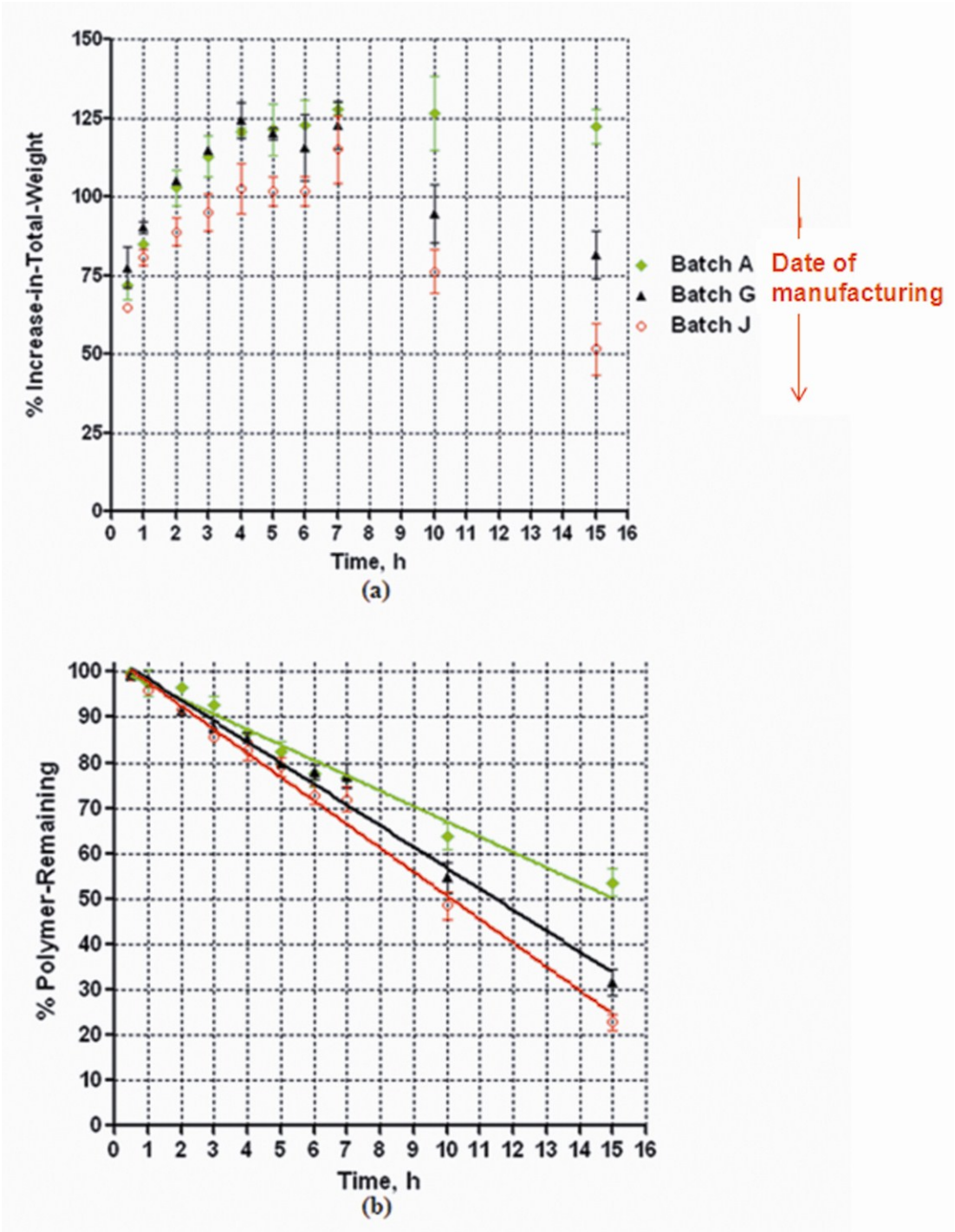
% Increase-in-Total-Weight
Time, h
(a)
Batch A
Batch G
Batch J
Date of manufacturing
% Polymer-Remaining
Time, h
(b)

Figure 46. The % Increase-in-total-weight (a) and % Polymer-remaining (b) of three batches of one grade of sodium alginate matrix tablets in deionized water at 37°C. Data are shown as mean and standard deviation of three replicates.

Table 24. Slope and R^2 values of the linear regression fit for the erosion profile of the three batches of sodium alginate.

Sodium Alginate	Slope*	r^2
Batch A	-3.38 ± 0.12	0.9640
Batch G	-4.62 ± 0.13	0.9771
Batch J	-5.23 ± 0.12	0.9846

* 95% confidence intervals (n=3).

The erosion behavior of these three batches of sodium alginate could be partially explained by their rheological properties in solution. Batch *A* has significantly higher apparent viscosities (2% w/w solution) and viscoelasticity (8% w/w) than batches *G* and *J*. As a result, batch A exhibits slower erosion rate and higher extent of water uptake than batches *G* and *J*. Batch *G* is not significantly different from batch *J* in apparent viscosity at low concentration (2% w/w) but is significantly higher in viscoelasticity at both low (2% w/w) and high (8% w/w) concentrations than batch *J*. The higher viscoelasticity of batch *G* leads to a slower erosion rate than batch *J*. At 15 h, batch *G* shows significantly higher % Increase-in-total-weight and % Polymer-remaining than batch *J*. Thus, those batches showing no significant differences in their apparent viscosities at low solution concentration could still differ in their swelling and erosion behavior due to their differences in viscoelasticity.

The overall hydrated polymer layer thickness as a function of time for sodium alginate matrix tablets prepared from three batches was plotted in Figure 47. The hydrated polymer layer increased at the beginning and kept almost constant after 5 h. Among the three batches, batch *A* has the largest hydrated layer thickness after 5 h. Batch *G* has similar thickness to batch *A* at 5 h and 10 h, but smaller thickness at 15 h. Batch *J* has the smallest thickness after 5 h. The hydrated polymer profile could be explained by the swelling and erosion behavior of these three batches. Batches with higher water uptake and slower erosion rate would show thicker hydrated layer thickness. However, the differences among the batches in hydrated layer thickness are not as pronounce as in water uptake profile.

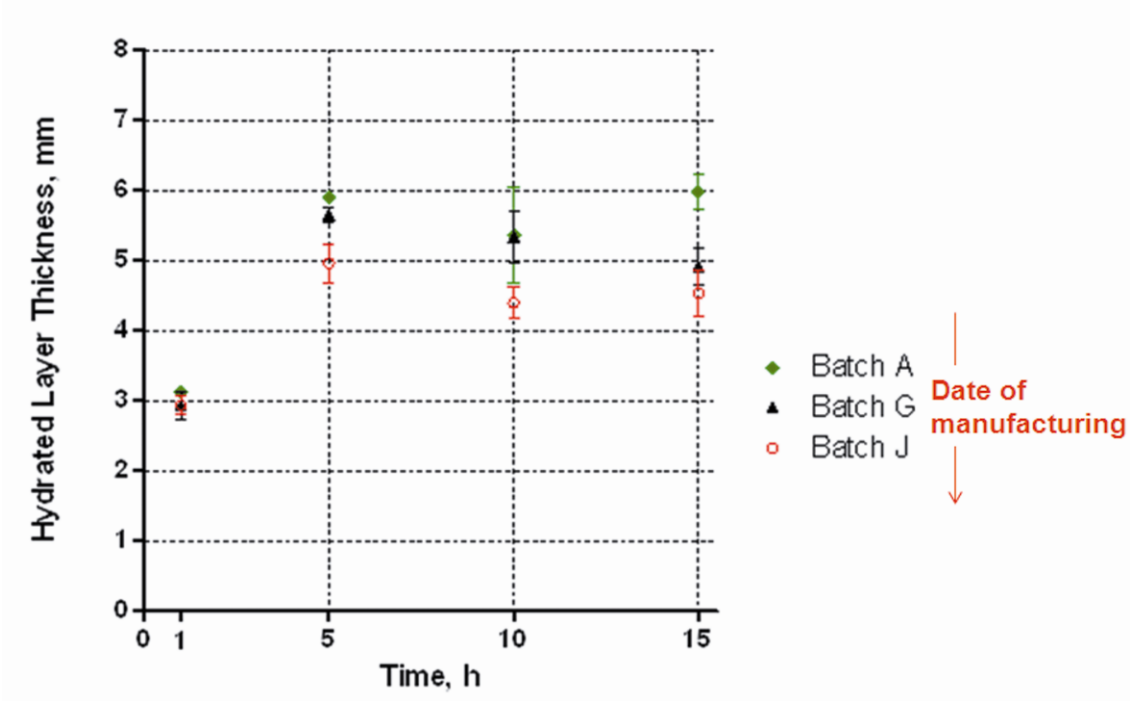

Figure 47. Hydrated polymer layer thickness as a function of time for sodium alginate matrix tablets of three batches of grade 3 during swelling.

The porosity of APAP-sodium alginate matrix tablets prepared from three batches is almost the same, varying from 0.15 to 0.16. The APAP release profile from sodium alginate matrix tablets prepared from three batches is shown in Figure 48. ANOVA test shows that batches *A* and *G* are not significantly different in their drug release profile ($P > 0.05$ at each time point). Batch *J* has higher percentage of drug released at each time point than batches *A* and *G* after 1 h ($P < 0.01$).

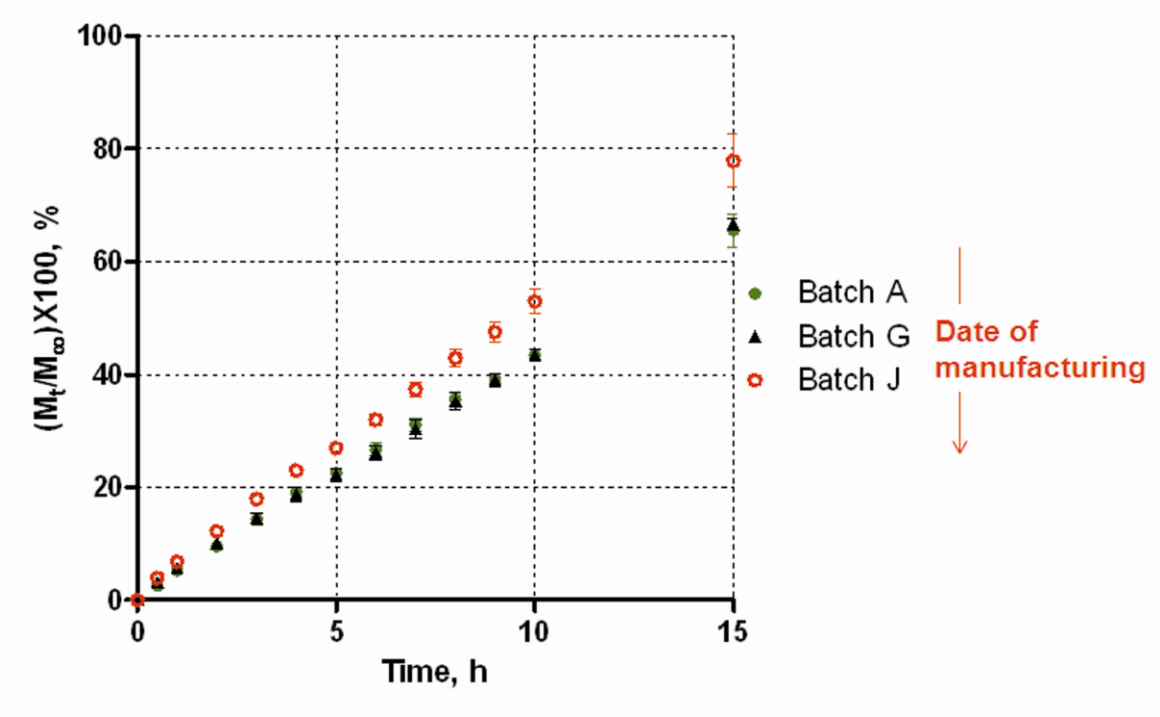

Figure 48. The APAP release profile from sodium alginate matrix tablets prepared from three batches.

APAP release from sodium alginate matrix tablets prepared from three batches is well described by the zero-order equation with $R^2 > 0.992$ (Table 25). :

$$\frac{M_t}{M_\infty} = kt, \qquad \text{Equation 41}$$

Table 25. The constant, k (reported as mean ± standard deviation based on three replicates) and R^2 values of the zero-order fitting of drug release data from sodium alginate matrix tablets prepared from three batches.

Sodium Alginate	k	R^2
Batch A	4.41 ± 0.03	0.996
Batch G	4.41 ± 0.03	0.995
Batch J	5.30 ± 0.04	0.992

The k values of batches *A* and *G* are almost the same, while the k value of batch *J* is higher than those of batches *A* and *G*. It is not surprising that tablets prepared from batch *J* shows the fastest drug release since matrix tablets of batch *J* has the highest erosion rate in water among the three batches. Although batch *A* matrix shows slower erosion than batch *G* matrix, the drug release profiles are the same between the two batches. The differences in apparent viscosity among the three batches are less than 50%, while the viscoelasticity of batch *G* in solution is in between batch *J* and batch *A*, and is closer to batch *A* than to batch *J*. The results suggested that, for multiple batches within a relatively narrow range of apparent viscosity, viscoelasticity of sodium alginate solutions could be more indicative of the drug release behavior from sodium alginate-based matrix tablets than the apparent viscosity. Recently, an abstract submitted to Society of Rheology also demonstrated that the viscoelastic properties of HPMC gels are correlated with the dissolution profile from HPMC matrix tablets prepared from multiple lots of HPMC with similar viscosity and chemical substitution.[185]

Conclusion

Significant differences in swelling and erosion behavior of sodium alginate matrix tablets were evident among different viscosity grades. Even different batches of the same grade exhibit significant differences in the swelling and erosion behavior of their matrix tablets. The significant differences in swelling behavior observed among different sodium alginate grades can be attributed to their significant differences in erosion behavior. The erosion behavior of sodium alginate matrix tablets can be partly explained by their rheological properties (both apparent viscosity and viscoelasticity) in solution. Sodium alginate with higher apparent viscosity and viscoelasticity in solution show slower erosion rate and higher swelling rate. Compacts prepared from grades or batches with higher viscosity and higher viscoelasticity show slower drug release. Apparent viscosities of sodium alginate solution at low concentration alone are not sufficient to predict the functionality of sodium alginate in matrix tablets. Viscoelastic properties of sodium alginate solutions at one high concentration indicative of polymer gel state are appropriate to be characterized as well.

CHAPTER 4. RELEVANCE OF RHEOLOGICAL PROPERTIES OF SODIUM ALGINATE IN SOLUTION TO CALCIUM ALGINATE GEL PROPERTIES

Introduction

Sodium alginate is a linear unbranched, amorphous copolymer composed of β-D-mannuronic acid (*M*) and α-L-guluronic acid (*G*) linked by 1→4 glycosidic bonds. The *M* and *G* units in the alginates may be randomly or non-randomly organized as heterogeneous or homogeneous sequences. Commercially available sodium alginate is usually extracted from various seaweeds. The chemical composition and sequence distribution of sodium alginate depends on the species and parts of the seaweed employed for extraction.[54] Chemical compositions for sodium alginate extracted from some common seaweed species have been discussed in **Chapter 1** and are listed in **Table 1**.[70]

Sodium alginate is widely used as a gelling agent due to its ability to form gels under mild conditions with divalent cations such as calcium. Calcium alginate gels have been used in wound dressings, dental impression materials, controlled release drug delivery systems, and the encapsulation of living cells.[90-93] The ionotropic gelation of sodium alginate with calcium cations is conventionally described by the "egg-box" model, where calcium cations interact with guluronic acid monomers in the cavities formed by pairing up of the *G* sequences of the alginate molecular chains.[87,88] Recent studies on calcium alginate gel formation reveal three distinct and successive steps of calcium binding to alginate with increasing calcium concentration: 1. interaction of calcium with a single *G* monomer; 2. formation of egg-box dimers; and, 3. lateral association of dimers to form multimers.[89] The *G* sequence and molecular weight of

sodium alginate determine the association modes of dimers and multimers of the resultant calcium alginate gels.[89]

Since sodium alginate is extracted from seaweed, commercial pharmaceutical grade alginates can be expected to be heterogeneous due to the differences in seaweed species, seaweed parts employed, harvesting location, and the harvesting season.[54] As a result, sodium alginates from different manufacturers are unlikely to exhibit the same properties. Furthermore, the alginates provided by a specific manufacturer could also have batch-to-batch variations as shown in the studies on inter-batch variability of sodium alginate reported in Chapter 2.

Pharmaceutical excipients are required to adhere to specifications listed in their monographs in United States Pharmacopeia-National Formulary (USP-NF). Each batch or lot of the excipient is tested by the excipient manufacturer to ensure compliance with the monograph specification; each shipment of the excipient would be accompanied by the manufacturer's certificate of analysis (CoA). However, pharmacopoeial specifications for sodium alginate make no mention of the viscosity of sodium alginate's solutions, even though the viscosity of its solutions is influenced by alginate molecular weight, *M* or *G* composition, and solution concentration. The manufacturer's CoA often provides viscosity data for sodium alginate solutions but seldom reports %G values for each batch. However, even when the manufacturer's viscosity data is provided, it is a "one-point" value, *i.e.*, determined at one concentration, one shear condition, and one temperature. Consequently, this datum may not reveal relevant rheological information regarding sodium alginate's behavior in alginate-containing formulations.

Previous studies on calcium alginate gels have shown that gel strength is influenced by both molecular weight and %G of the sodium alginate: higher molecular weights or higher %G are usually associated with stronger gels.[61-63,186-188] For those sodium alginates with similar %G, it was reported that higher molecular weights or higher solution apparent viscosities correlated with higher calcium alginate gel strength.[186-188] However, no quantitative relationship among gel strength, apparent viscosity, molecular weight, and/or %G was proposed or suggested. Furthermore, most of the sodium alginates employed in these studies were not pharmaceutical grade.

Data presented in earlier chapters demonstrated that rheological methods, including steady shear and small amplitude oscillation, are capable of differentiating among multiple pharmaceutical grades and batches of sodium alginate varying in average molecular weight and chemical composition. Furthermore, the "one-point" viscosity values reported in the CoAs do not reflect the inter-batch variability in the solutions' apparent viscosities at 2% w/w. The purpose of this work is to determine whether sodium alginate solutions' rheological parameters are meaningful relative to the subsequent use of the various sodium alginates in the formulation of calcium alginate gels. Calcium alginate samples were prepared from 2% w/w solutions of the six grades and ten batches of sodium alginate previously studied. Gel properties were evaluated by compression using an Instron Universal Testing Machine and the correlation between the gel properties and the solution properties of sodium alginate was investigated.

Materials and Methods

Materials

Six grades (one batch each) and ten batches of one of the grades of sodium alginate were provided by FMC Biopolymer (Drammen, Norway). Physicochemical properties of the various grades and batches are listed in Tables 6 and 9 in **Chapter 2**, respectively. Apparent viscosity of alginate solutions increases from grade 1 to grade 6. Multiple batches of sodium alginate were designated as batches *A* to *J* on the basis of their date of manufacture, with batch A as the earliest batch. Deionized water was obtained from a *Milli-Q* ultrapure water system (Millipore Corp., Billerica, MA, USA). Calcium phosphate dibasic dihydrate and gluconic acid-δ-lactone were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as supplied.

Methods

Rheological Measurements of Sodium Alginate Solutions

The procedures employed in generating the steady shear and small amplitude oscillatory data for the sodium alginate solutions were described in the materials and methods section in Chapter 2.

Calcium Alginate Gel Preparation

Calcium alginate gels were prepared by the "internal gelification" method.[187,189] An amount of calcium ion (calcium phosphate dibasic dihydrate) equivalent to one-half the alginate monomer molar content ($n_{ca^{2+}}=1/2\ n_{monomer}$[i]) was thoroughly dispersed in 2% w/w sodium alginate solutions. The dispersions were mixed at 2000 rpm for 2 min *via* a

[i] The number of moles of sodium alginate monomers ($n_{monomer}$) can be calculated as $m_{alginate}$/(198g/mole).

Thinky Mixer (Model ARM 310, Thinky USA, Laguna Hills, CA, USA) to remove air bubbles. By adding equivalent molar amounts ($n = n_{Ca^{2+}}$) of gluconic acid-δ-lactone to the dispersion under vigorous stirring, calcium ions were slowly released into the solution. The resultant dispersions were quickly poured into a 24-well plate (Falcon® 3047 Multiwell™, Becton Dickinson Labware, Franklin Lakes, NJ, USA) and stored at room temperature for 24 h. Cylindrical gel samples were formed inside the wells (~15 mm in diameter x 17 mm in height).

Mechanical Tests

Cylindrical gel samples were subjected to compression to fracture at a cross-head speed of 120 mm/min on an Instron Universal Testing Machine (model 5869) equipped with a 1 kN load cell (Instron, Norwood, MA, USA) (Figure 49). Instron software, Bluehill®2, was used to operate the instrument and collect data. The cross-head and base were both covered with sandpaper (fine grade 150, 3M, St. Paul, MN, USA) to prevent gel slippage between the platens. All tests were replicated six times, and the mean values and standard deviations calculated.

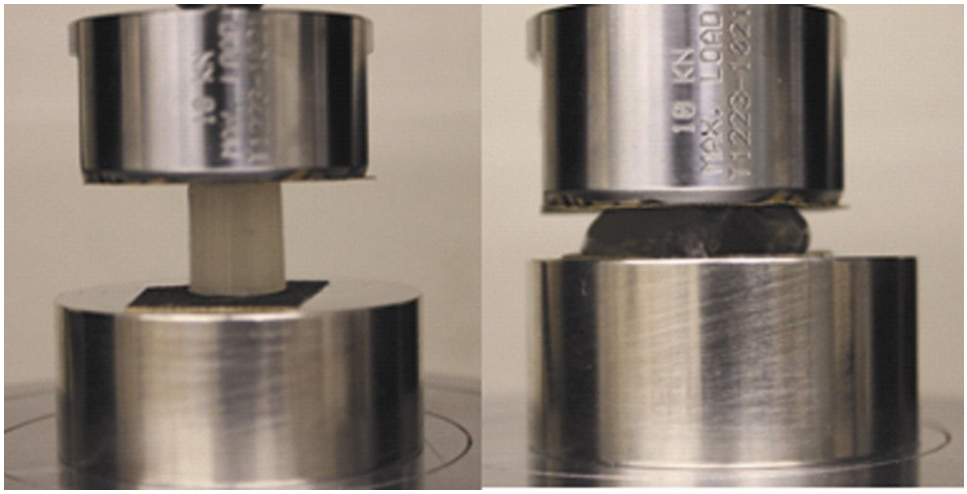

Figure 49. Illustration of cylindrical gel sample placed between two platens on an Instron Universal Testing Machine (Left: beginning of compression; Right: gel fracture under compression).

Data Analysis

During compression, the cylindrical gel sample became barrel-shaped due to the friction at the interfaces between the gel sample and the cross-head. Although the barreling deformation is indicative of a non-uniform deformation (*i.e.*, the stress and strain vary throughout the gel sample under compression), the measurement of the localized fracture properties of a material can still provide useful information.[190] With barreling, for a given axial compressive strain, the barrel shape of the deformed samples provides circumferential strain at the equator that is greater than the strain that would arise during homogenous compression. Meanwhile, the local compressive strain at the equator is less than the strain that would arise during homogenous compression. These strain combinations lead to tensile stress around the circumference and reduced compressive stress at the barrel equator. Therefore, compression tests with friction, and consequent barreling, can be used as tests for fracture. Fracture occurs catastrophically by shear either along one large shear plane, leading to complete separation, or at several sites around the specimen, leading to crushing of the material. In either case, the load-carrying capacity of the material is abruptly terminated at this maximum compression force.[190] As a result, the maximum compression force, F_M, along with the engineering strain, ε_E, at fracture was used to compare the calcium alginate gel properties prepared from various grades and batches. Engineering strain is defined as:

$$\varepsilon_E = \frac{H_0 - H(t)}{H_0}, \qquad \text{Equation 42}$$

where H_0 is the initial height of the cylindrical gel sample, and $H(t)$ is the instantaneous value of the sample height at fracture.

Statistical Analysis

The differences in calcium alginate gel properties among the various grades and batches were analyzed via analysis of variance (ANOVA) and Levene's test for homogeneity of variance using PASW Statistics 18 for Windows (SPSS Inc., Chicago, IL, USA). *Post hoc* testing ($p < 0.05$) of the multiple comparisons was performed by either the Tukey HSD (Honestly Significant Difference) test or Games–Howell test depending on whether Levene's test was insignificant or significant, respectively. Partial correlation tests for gel properties and rheological properties of sodium alginate solutions were conducted using PASW Statistics 18 for Windows (SPSS Inc., Chicago, IL, USA).

Results and Discussion

Inter-Grade Variability

All gel samples prepared from the six grades of sodium alginate exhibited syneresis after 24 h at room temperature. The actual alginate concentration in the gel samples was estimated taking into account the loss of free water. The actual and nominal concentrations are quite similar among the six grades of sodium alginate; their ratio averaged 1.06 ± 0.02, similar to the ratio reported by Mancini *et al.*[187] for their calcium alginate gels.

Table 26 summarizes the engineering strain (ε_E), and the maximum compression force (F_M) at gel fracture for calcium alginate gels prepared from six different grades of sodium alginate. Generally, stronger gels require larger force and larger strain to fracture. Gels prepared from grades 1 and 2 have smaller ε_E and F_M at fracture than gels prepared from the other four grades. Gels prepared from grades 3, 4, 5, and 6 show similar ε_E, but different F_M at fracture. ANOVA and *post hoc* multiple comparisons tests of the F_M at gel fracture among the six grades reveal that grades 5 and 6 are not significantly different from each other while the other grades do differ significantly from one another ($p < 0.01$).

Table 26. Engineering strain (ε_E), and the maximum compression force (F_M) at gel fracture for calcium alginate gels prepared from six different grades of sodium alginate.

Grade	ε_E*	F_M **(N)***
1	0.53 ± 0.006	44.30 ± 1.58
2	0.52 ± 0.005	22.05 ± 0.81
3	0.58 ± 0.004	60.94 ± 1.38
4	0.60 ± 0.015	84.88 ± 5.43
5	0.59 ± 0.004	120.51 ± 2.91

6	0.61 ± 0.012	118.35 ± 12.25

*n=6

The relationship of calcium alginate gel strength (F_M) to the %G of sodium alginate and the rheological properties (η_{app} and tan δ) of the sodium alginate solutions were analyzed by partial correlation tests *via* PASW Statistics 18. Among the grades with similar %G, *i.e.*, grades 1, 3, and 4, there is a significant positive correlation between F_M and η_{app} ($r = 0.752$, $P < 0.001$). These three grades show substantial differences in their apparent viscosity as discussed in Chapter 2. The differences in apparent viscosity are mainly due to their differences in molecular weight, *i.e.*, high apparent viscosity is associated with high molecular weight. Since grades 1, 2, and 4 are similar in %G, the grades with higher apparent viscosity (or higher molecular weight) would tend to have longer homogeneous G sequence that is involved in the gel formation. As a result, grades with a higher apparent viscosity result in calcium alginate gels with higher strength.

However, the results for the partial correlation analysis for all six grades of sodium alginate show that F_M is significantly correlated with %G ($r = 0.893$, $P < 0.001$), but not with the rheological properties of the sodium alginate solutions ($r = -0.147$, $P = 0.400$). It suggests that %G plays a more important role in determining the gel strength. Grade 5 has a much higher %G than both grade 4 and grade 6. It is expected that gels formed from grade 5 are stronger than gels formed from grade 4. Although grade 5 has a smaller molecular weight than grade 6, the higher %G compensates the smaller molecular weight, probably resulting in similar homogeneous G sequence distribution and

eventually similar gel strength between these two grades. As a result, for multiple grades with substantial differences in %G, apparent viscosity of sodium alginate in solution is not sufficient to predict the resultant calcium alginate gel properties.

Inter-Batch Variability

Gel samples prepared from multiple batches of sodium alginate exhibited syneresis after 24 h at room temperature. The ratio between the actual and nominal concentration is almost the same among the multiple batches (1.08 ± 0.03). Gel compression properties of the ten batches are summarized in Table 27.

Table 27. Engineering strain (ε_E), and the maximum compression force (F_M) at gel fracture for calcium alginate gels prepared from ten batches of one grade of sodium alginate.

Batch	$\boldsymbol{\varepsilon_E}$*	$\boldsymbol{F_M}$**(N)***
A	0.55 ± 0.006	53.10 ± 0.82
B	0.54 ± 0.013	45.71 ± 3.10
C	0.57 ± 0.008	59.85 ± 2.11
D	0.56 ± 0.005	59.53 ± 1.83
E	0.56 ± 0.007	58.88 ± 1.52
F	0.56 ± 0.008	57.73 ± 1.97
G	0.57 ± 0.007	59.95 ± 2.09
H	0.57 ± 0.005	58.43 ± 1.45

I	0.58 ± 0.005	69.95 ± 0.91
J	0.57 ±0.006	68.64 ±2.33

***n=6**

The ε_E values at gel fracture range from 0.54 to 0.58 among these batches. The gel samples with the smallest ε_E at fracture also have the lowest F_M at fracture. Since the %G values for these batches are in the similar range (37-41%), it would be expected that batches with higher apparent viscosities in solution would result in calcium alginate gels with higher gel strength. Previous studies of the rheological properties of the ten batches of sodium alginate demonstrated that the η_{app} of batch *A* (2% w/w solutions at 25°C) is significantly higher than that of the other batches, while no significant differences are evident among the other 9 batches. However, batch *A* exhibits the second lowest gel strength among the multiple batches. Batches *J* and *K* exhibit much higher gel strength than other batches. As a result, the apparent viscosities of the sodium alginate solutions from multiple batches are not indicative of the resultant calcium alginate gel strength as depicted in Figure 50. On the other hand, the viscoelastic behavior of the multiple batches demonstrates a significant, although minimal, correlation (Figure 51, $r = 0.553$, $P < 0.001$) between F_M and tan δ.

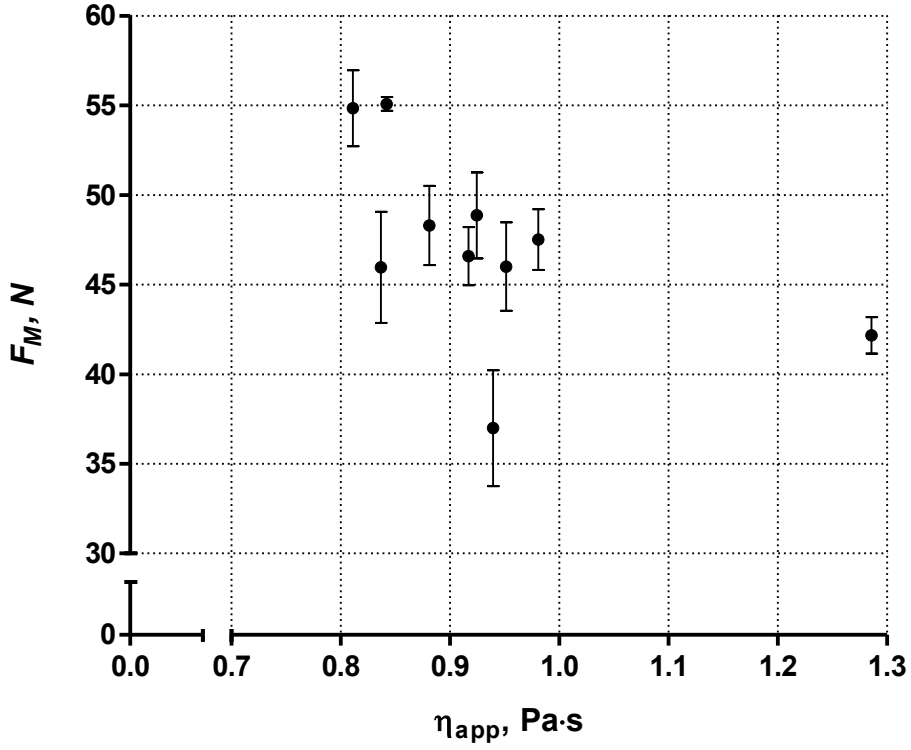

Figure 50. The maximum compressive force of calcium alginate gel samples prepared from the multiple batches of grade 3 as a function of the corresponding apparent viscosity (η_{app}) of sodium alginate solutions (2% w/w, 1 Pa shear stress, 25°C).

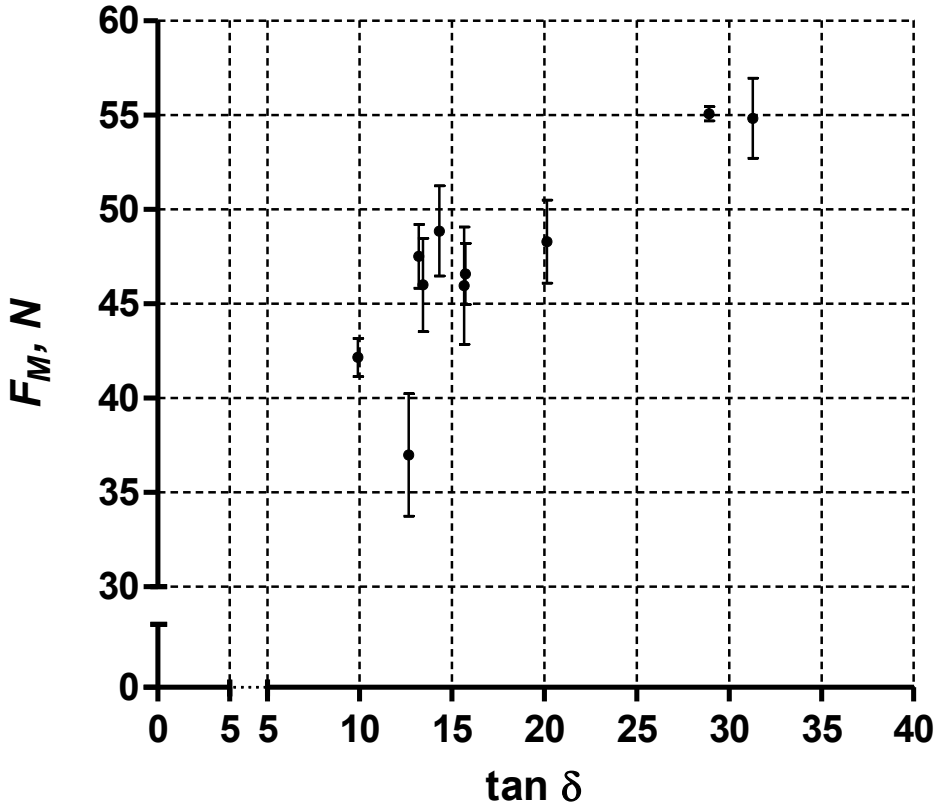

Figure 51. The maximum compressive force of calcium alginate gel samples prepared from the multiple batches of grade 3 as a function of the corresponding tan δ of sodium alginate solutions (2% w/w, 1 rad/s, 25°C).

ANOVA test on F_M for the multiple batches demonstrated significant differences among batches ($P < 0.001$). The subsequent multiple comparisons test yields the information on the pair-to-pair differences as summarized in Table 28 along with their differences in rheological properties. Batches that are significantly different in η_{app} are not necessarily significantly different in calcium alginate gel properties. Those batches that are significantly different in their tan δ values are also significantly different in their

F_M values. Still, there are batches that are not significantly different in their tan δ values but significantly different in their F_M values. Apparently, batches show more significant differences in their gel properties than in their rheological properties.

Table 28. Results for multiple comparisons test of the gel deformation work and rheological properties among the ten batches of sodium alginate (grade 3).

Batch										
A	**A**									
B	**η**	**B**								
C	**η,t,g**	**g**	**C**							
D	**η,g**	**g**	**—**	**D**						
E	**η**	**g**	**—**	**—**	**E**					
F	**η**	**g**	**—**	**—**	**—**	**F**				
G	**η,g**	**g**	**—**	**—**	**—**	**—**	**G**			
H	**η,g**	**g**	**—**	**—**	**—**	**—**	**—**	**H**		
I	**η,t,g**	**t,g**	**g**	**t,g**	**g**	**t,g**	**t,g**	**t,g**	**I**	
J	**η,t,g**	**t,g**	**g**	**t,g**	**t,g**	**t,g**	**t,g**	**t,g**	**—**	**J**

The letters in the cells correspond to significant differences in paired data for specific rheological outcomes or gel properties, as follows:

η - log η_{app} ; t – tan δ ; g - F_M ; **—** - No significant differences.

Inadequate knowledge of the monomer sequence and distribution of the alginate molecular chains complicates the interpretation of these data.[191] While solid-state NMR can be used to determine the total amount of each monomer in intact sodium alginate powder, it cannot be easily used to determine the amounts of diad and triad sequences due to the broad linewidths and decreased resolution typically seen in amorphous materials. Even though solution NMR spectroscopy has been applied to estimate the monad (G or M), diad (GG, MM, or MG), and triad (GGG, GGM, MGG, MGM, *et al*) frequencies within the alginate molecule,[68,69] it requires partial acid hydrolysis of the sodium alginate sample which could lead to sample alteration or loss of part of the polymer chain. Furthermore, assuming the data obtained from solution NMR were accurate, the monomer sequence length distribution can only be obtained by simulation assuming a statistical model for monomer distribution, which is usually an oversimplification of the biosynthesis of alginate.[72] Commercially available sodium alginates are very likely produced from different types or parts of seaweeds and blended together to achieve a final chemical composition. In these situations, NMR data with statistical models are not sufficient to depict the monomer sequence length distribution.[64]

It was reported that a minimum length of *G* sequence is required to form junction with divalent cations (about 8 for calcium alginate gel at 20°C) and longer *G* sequence results in stronger gels.[64-66] In addition, molecular weight distribution of sodium alginate would influence the interactions of dimers and multimers of the resultant calcium alginate gels.[89] The variability in *G* sequence and molecular weight distribution among these grades and batches may not be directly reflected in the rheological properties of sodium

alginate solutions. Therefore, it is difficult to predict the calcium alginate gel properties based on the rheological properties of sodium alginate solutions.

As a result, for calcium alginate gel formulations, *e.g.*, calcium alginate hydrogels, microcapsules, etc., it is recommended that calcium alginate gel properties, such as maximum force at gel fracture, be used to define the design space.

Conclusion

The mechanical strength of calcium alginate gels prepared from multiple grades is significantly correlated with %G of the corresponding sodium alginates. However, the rheological properties of solutions of these different grades of sodium alginate are not indicative of the resultant gel properties. For the one specific grade of sodium alginate available in multiple batches, inter-batch differences in solution rheological properties were insufficient to predict the corresponding calcium alginate gel's mechanical properties. As a result, the use of steady shear and SAO methods to characterize sodium alginate solutions do not offer adequate insight into the resultant calcium alginate gel properties. Other rheological methods such as extensional rheology may ultimately prove to be more effective and meaningful. In the interim, until additional studies are done, we recommend that calcium alginate gels' mechanical properties be measured directly in order to ensure interchangeability of new batches or lots of sodium alginate used in gel preparation.

CHAPTER 5. CONCLUSION

This dissertation work investigated the inter-grade and inter-batch variability of sodium alginate with a focus on rheological properties of sodium alginate solutions, compression properties of sodium alginate powders, the functionality of sodium algiante in matrix tablets, and the mechanical properties of calcium alginate gels,.

As discussed in Chapter 1, rheological properties of polymeric excipients are important parameters that can be related to their functionality in different drug dosage forms and delivery systems. In Chapter 2, steady shear and small amplitude oscillation measurements have been performed on solutions of six grades of sodium alginate over a wide range of shear stresses and angular frequencies. Steady shear results suggest that the apparent viscosities of solutions of different grades of sodium alginate are influenced by both molecular weight and uronic acid composition: higher molecular weight and higher %G are likely to result in higher apparent viscosities. Rheological evaluations of multiple batches of one grade of sodium alginate produced in the same year showed significant batch-to-batch variability in steady shear behavior. Thus, it is recommended that for sodium alginate used as a thickening or binding agent, the apparent viscosities or rheograms of its solutions under appropriate shear conditions could be used to ensure inter-manufacturer, inter-grade, and inter-batch interchangeability of sodium alginate.

As sodium alginate solution concentrations are increased, the rheological behavior of the solutions changes from that of a liquid to that of a weak physical gel. The "one-point" apparent viscosity data for various grades of sodium alginate are not reflective of their complex rheological properties at high concentrations. Thus, for sodium alginate used in alginate-based matrices, we recommended that both steady shear behavior of its

solutions at low concentration (*e.g.*, 2% w/w) and the viscoelastic properties of its solutions at high concentratioin indicative of polymer gel state (*e.g.*, 8% w/w) should be employed to ensure the interchangeability of different grades and batches of sodium alginate.

In Chapter 3, the inter-grade and inter-batch variability of sodium alginate in matrix tablets was investigated. First, the compression behavior of various grades and batches of sodium alginate was studied by compaction energetics, Gurnham analysis, and Heckel analysis with microcrystalline cellulose (MCC PH102) and lactose anhydrous used as reference materials. It was found that sodium alginates deform less plastically than MCC PH102 but slightly more plastically than lactose anhydrous. Sodium alginates also demonstrate more elastic deformations during compression than both MCC PH102 and lactose anhydrous. Three batches from the same grade were found to vary in their compressibility but are identical in compactibility.

The swelling and erosion behavior of sodium alginate tablets prepared from four grades and three batches were determined and the relevance to their rheological behavior was investigated. Significant differences in swelling and erosion behavior of sodium alginate matrix tablets were evident among different viscosity grade grades. The significant differences in swelling behavior observed can be attributed to their significant differences in erosion behavior. The erosion behavior of sodium alginate matrix tablets could be partly explained by the rheological properties of the corresponding sodium alginate solutions. Sodium alginate with higher apparent viscosity and viscoelasticity in solution show slower erosion rate and higher swelling rate. Acetaminophen release (one-dimentional release) from sodium alginate matrix tablets can be described by a zero-order

equation. Compacts prepared from higher vicosity grades showed slower drug release profiles. Compacts prepared from batches with higher viscoelasticity demonstrated slower drug release profiles. Apparent viscosities of sodium alginate solution at low concentration alone are not sufficient to predict the functionality of sodium alginate in matrix tablets. Viscoelastic properties of sodium alginate solutions at one high concentration indicative of polymer gel state ought to be characterized as well.

Chapter 4 explores the relevance of rheological properties of sodium alginate in solution to the mechanical properties of calcium alginate gels prepared from the six grades of sodium alginate and ten batches of one grade. The mechanical strength of calcium alginate gels prepared from multiple grades was found to be significantly correlated with %G of the corresponding sodium alginates. However, the rheological properties of solutions of these different grades of sodium alginate are not indicative of the resultant gel properties. For the multiple batches of the same grade, inter-batch differences in the rheological behavior were insufficient to predict the corresponding calcium alginate gel's mechanical properties even though there is a significant but minimal, correlation between gel property and tan δ. As a result, the use of steady shear and small amplitude ocscillation methods to characterize sodium alginate solutions do not offer adequate insight into the resultant calcium alginate gel properties. Thus, it is recommended that calcium alginate gels' mechanical properties be measured directly in order to ensure interchangeability of new batches or grades of sodium alginate used in gel preparation.

Overall, the results obtained from this dissertation work demonstrate the advantages of characterizing the inter-grade and inter-batch variability of sodium alginate

using appropriate rheological methods, such as steady shear and small amplitude oscillation, over the "one-point" apparent viscosity data. Rheological methods, including steady shear and small amplitude oscillation, could be very useful in characterizing sodiunm alginate used in formulations as thickener, binder, and/or controlled release agent. However, the inter-grade and inter-batch variability reflected in rheological properties was not directly correlated with the variations in the mechanical properties of calcium alginate gels. Calcium alginate gels' mechanical properties should be measured directly in order to ensure interchangeability of new batches or lots of sodium alginate used in gel preparation.

The results obtained in this dissertation research strongly suggest that it is important for formulation scientists to determine the influence of inter-grade and inter-batch variability on the pharmaceutical products under development. Different grades and multiple batches of the same grade can be obtained from the excipient manufacturer for formulation development. In case the inter-batch variability of the commercially available batches results in substantial differences in the performance of the final products, a tighter control of variability is perferred. For sodium alginate, viscoelastic properties of sodium alginate solutions obtained in various steps in the extraction process can be used to help control the inter-batch variability within a tighter range than that observed in current commercial batches. Based on experimental design and data analysis, a combination of extraction parameters could be determined to produce sodium alginate with acceptable variability for a specific pharmaceutical product. It is critical for formulation scientists to maintain good communication with the excipient suppliers about the desired excipient properties. Both parties should have the same understanding of the

critical attributes of the excipients and the acceptable variability of a specific grade of excipient for a specific product. Furthermore, rheological properties of certain liquid pharmaceutical products (*e.g.*, suspension, emulsions, etc) can be monitored duirng processing/manufacturing in order to minimize the variability in final product performance. Certain rheometers, *e.g.*, RheoSense, a slit rheometer, could be applied for the on-line measurement of the apparent viscosity of liquid products during processing or manufacturing.

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APPENDIX I. Rheological Characterization of Sodium Alginate

This section describes the detailed methodology used to generate the rheological data as listed in chapter 2, along with the validation data.

Steady shear measurements were performed on AR 2000 rotation rheometer with cone-and-plate (TA Instruments, New Castle, DE, USA) using stepped flow procedure. Stress was varied from 1 to 100 Pa, and shear rate data were collected at 11 stress values, *i.e.*, 5 points in each decade based on log-scale: 1.0 Pa, 1.6 Pa, 2.5 Pa, 4.0 Pa, 6.3 Pa, 10.0 Pa, 15.8 Pa, 25.1 Pa, 39.8 Pa, 63.1 Pa, and 99.9 Pa. At each stress, the measuring time for shear rate is 30 seconds and the shear rate is reported as the average of data obtained in the last 10 seconds. The instrument is periodically validated by a Newtonian standard, Cannon viscosity standard N35 (Cannon Instruments, State College, PA, USA). The apparent viscosity data of N35 obtained by AR 2000 rheometer from 2007-2009 are shown in Figure 52. The determined apparent viscosity values are within the ±5% range of the standard viscosity value (0.056 Pa·s).

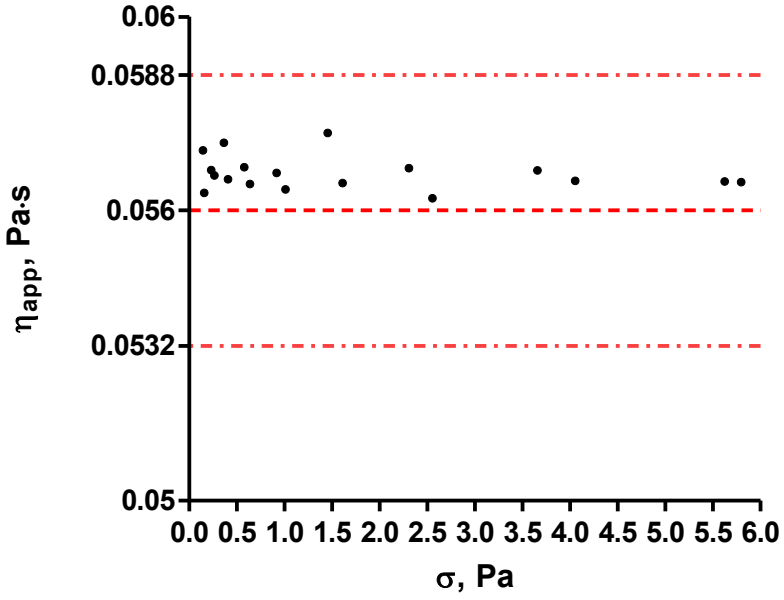


Figure 52. The apparent viscosity values of N35 at 25°C determined by AR2000 rotational rheometer.

For small amplitude oscillation measurements, the rheometer was validated by performing frequency sweep measurements (1-100 rad/s at 10% strain) on a standard material ─ isoprene liquid rubber (LIR50), a linear monodisperse 1,4-polyisoprene with a molecular weight of 45 kDa and polydispersity less than 1.1 (Kuraray American, Inc., Houston, TX, USA). The viscoelastic data (G′ and G″) obtained on AR 2000 rotational rheometer are depicted in Figure 53. The G′ and G″ in the angular frequency ranging from 1 to 10 rad/s are fitted by power-law equation:

$$G' = a \cdot \omega^{b}$$
$$G'' = c \cdot \omega^{d}, \qquad \text{Equation 43}$$

The constant values are reported in Table 29. The experimental *b* and *d* values for liquid isoprene rubber (LIR50) based on the viscoelastic data obtained on AR 2000 rheometer are within 5% deviation from the theoretical value for liquids, *i.e.*, *b*=2, and *d*=1.[192]

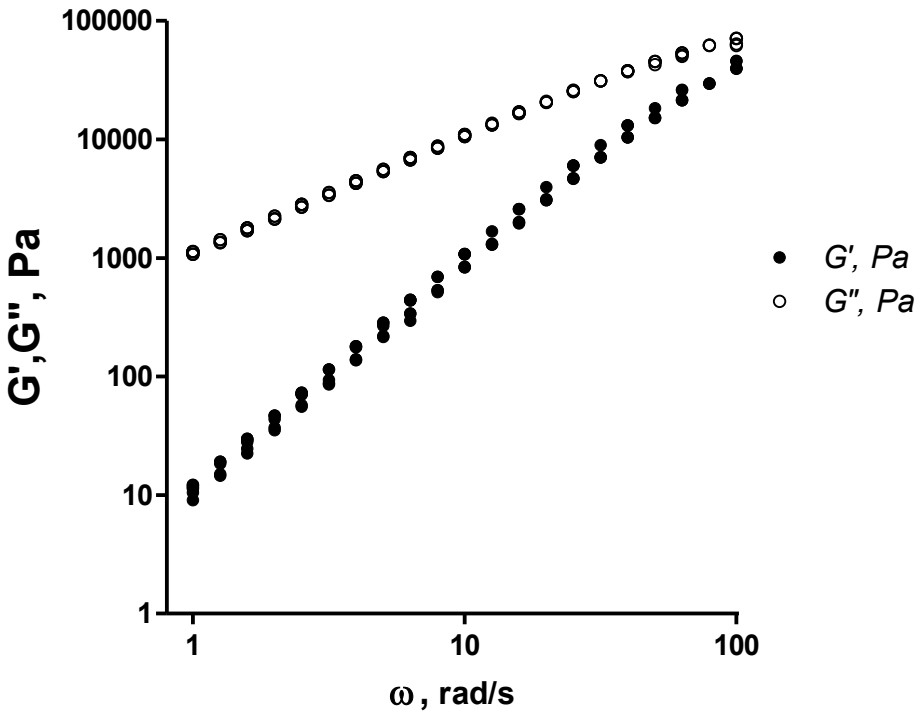


Figure 53. The G′ and G″ data of liquid isoprene rubber determined on AR 2000 rotational rheometer.

Table 29. The constants of the power law equations for G′ and G″.

a	10.3 ± 1.5
b	2.0 ± 0.07
c	1113.0 ± 13.0
d	1.0 ± 0.006

Strain sweeps were carried out to determine the linear viscoelastic region of sodium alginate solutions. Strain sweeps were performed from 1 to 100% (or 1 to 20%) at

1 rad/s, or 10 rad/s, or 100 rad/s. Results for the six grades and ten batches are shown from Figure 54 to Figure 62. The linear viscoelastic range is experimentally determined as the strain range where G' value remains approximately the same until more than a 10% drop of G' occurs when strain exceeds a critical value. All sodium alginate solutions are in the linear viscoelastic range when the strain was 10%, based on the results of strain sweep measurements.

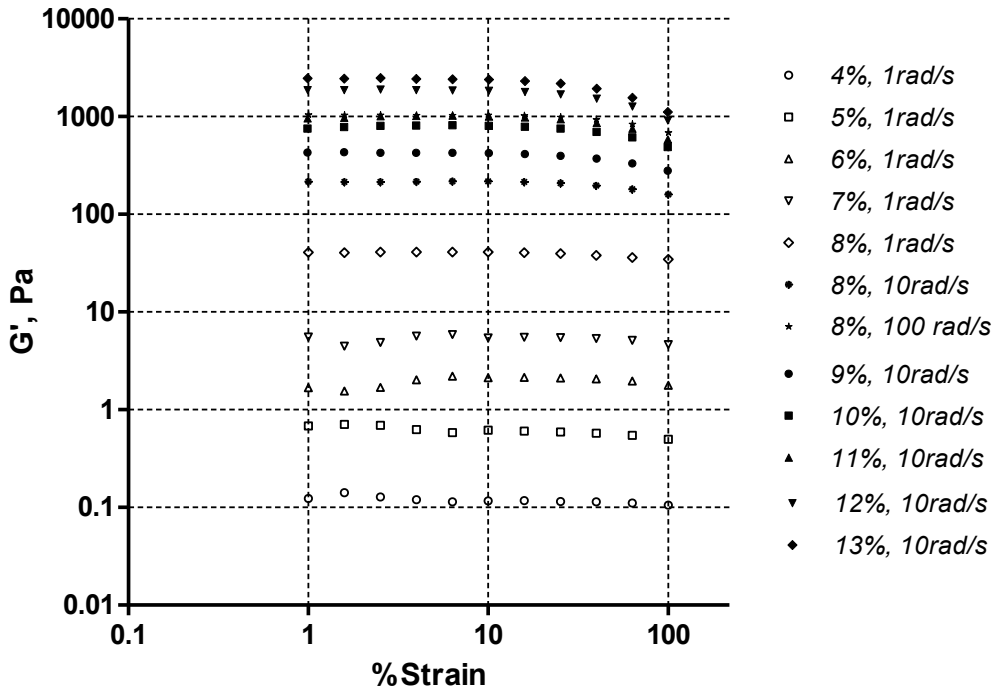


Figure 54. The strain sweep result for sodium alginate Grade 1 (LF 10/60LS) solutions.

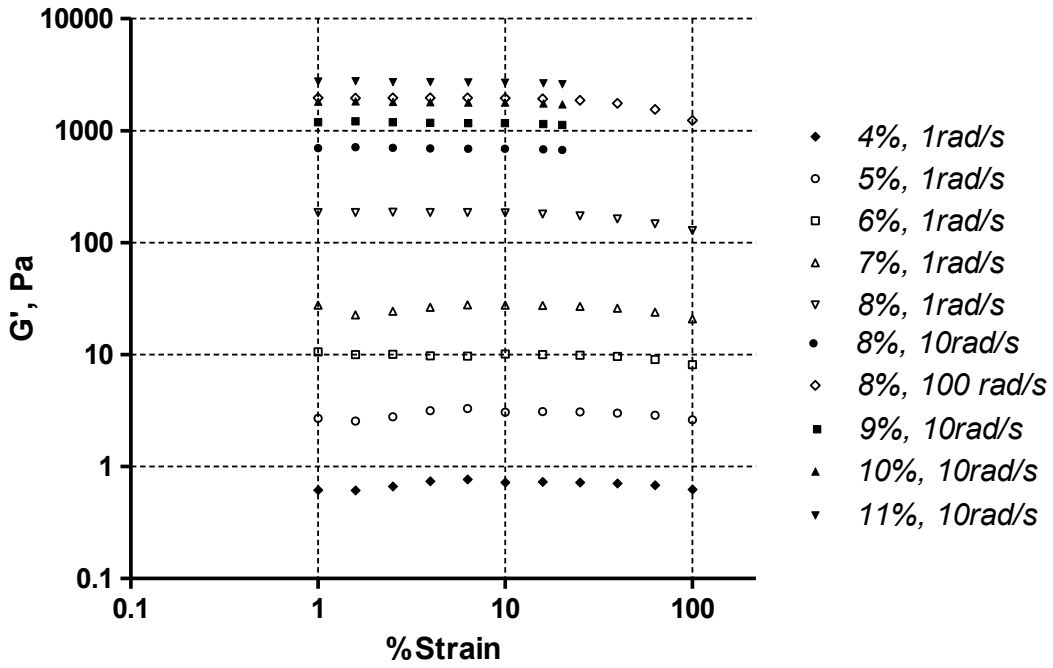


Figure 55. The strain sweep result for sodium alginate Grade 2 (LF 240D) solutions.

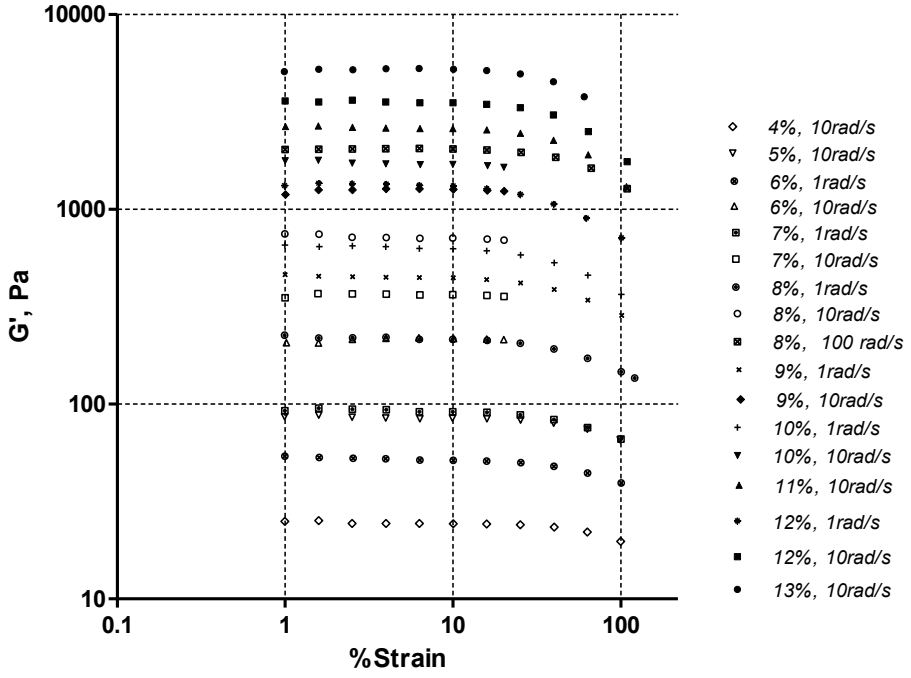


Figure 56. The strain sweep result for sodium alginate Grade 3 (LF 120M) solutions.

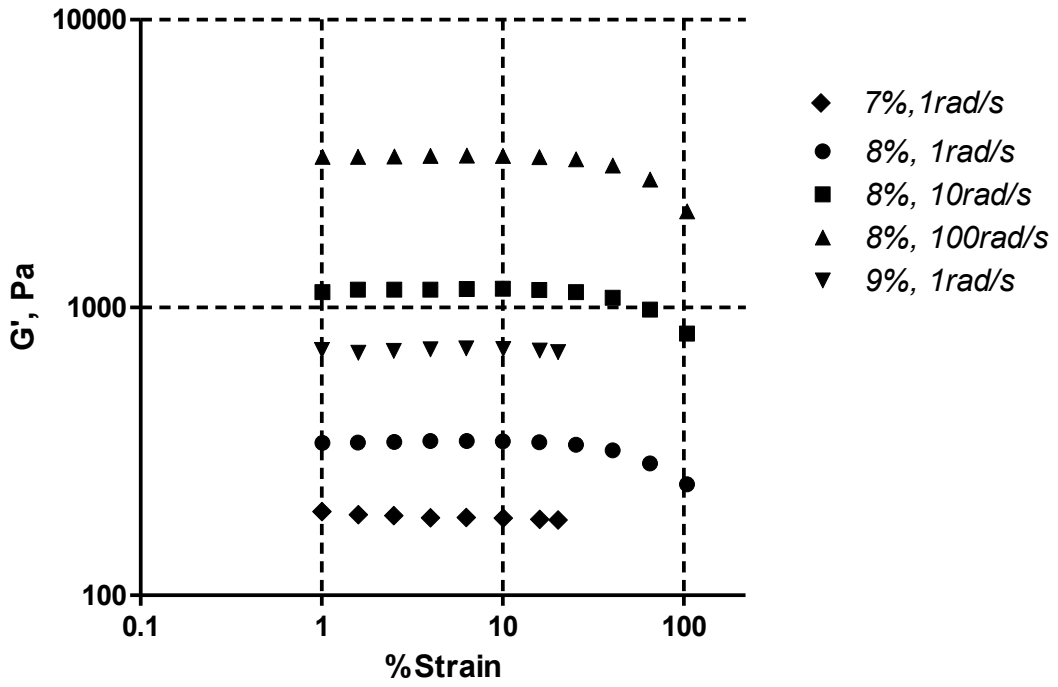


Figure 57. The strain sweep result for sodium alginate Grade 4 (LF 200M) solutions.

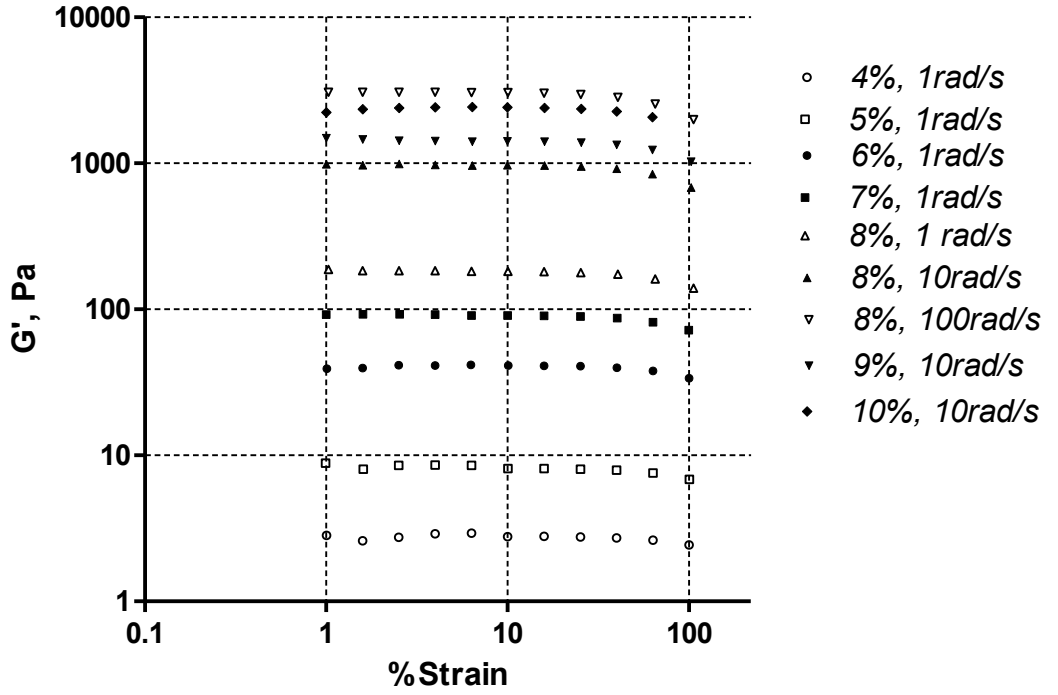


Figure 58. The strain sweep result for sodium alginate Grade 5 (LF 200DL) solutions.

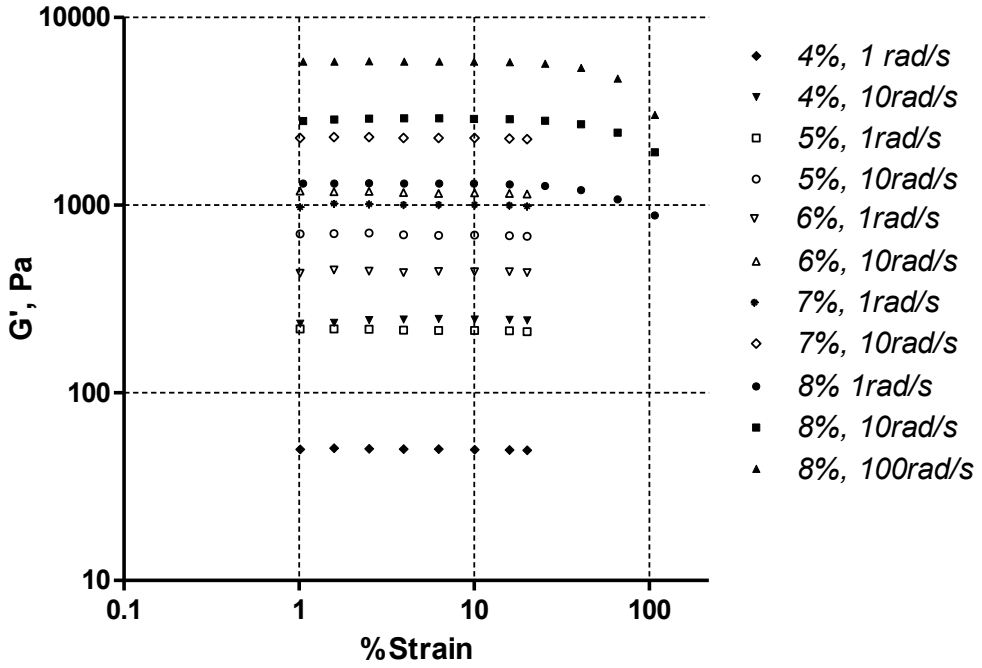


Figure 59. The strain sweep result for sodium alginate Grade 6 (HF 120RBS) solutions.

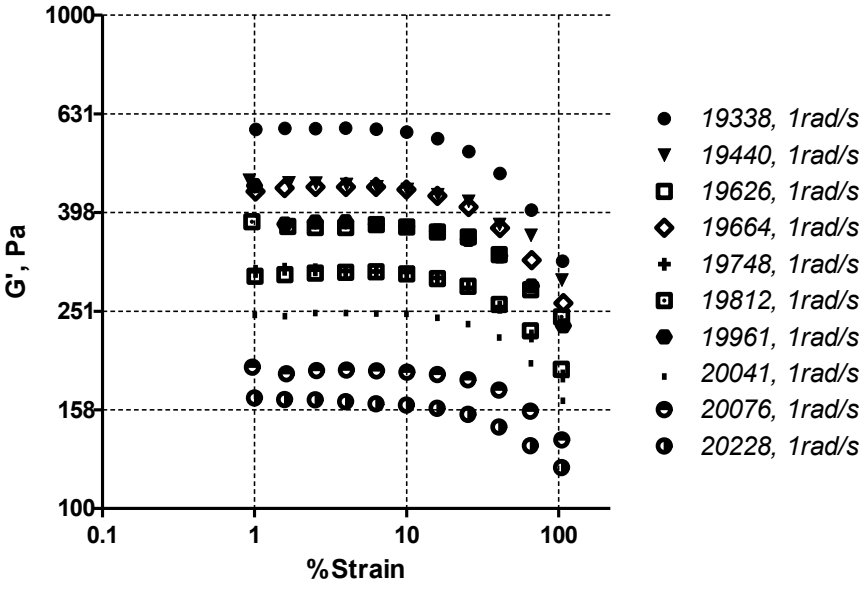


Figure 60. The strain sweep result at 1 rad/s for sodium alginate solutions (ten batches of LF120M at 8% w/w and 37 °C).

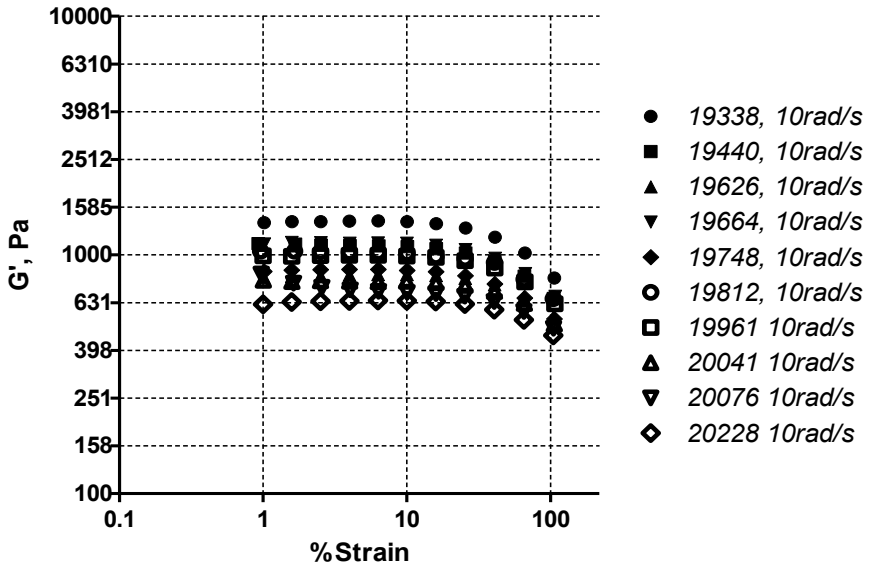


Figure 61. The strain sweep result at 10 rad/s for sodium alginate solutions (ten batches of LF120M at 8% w/w and 37 °C).

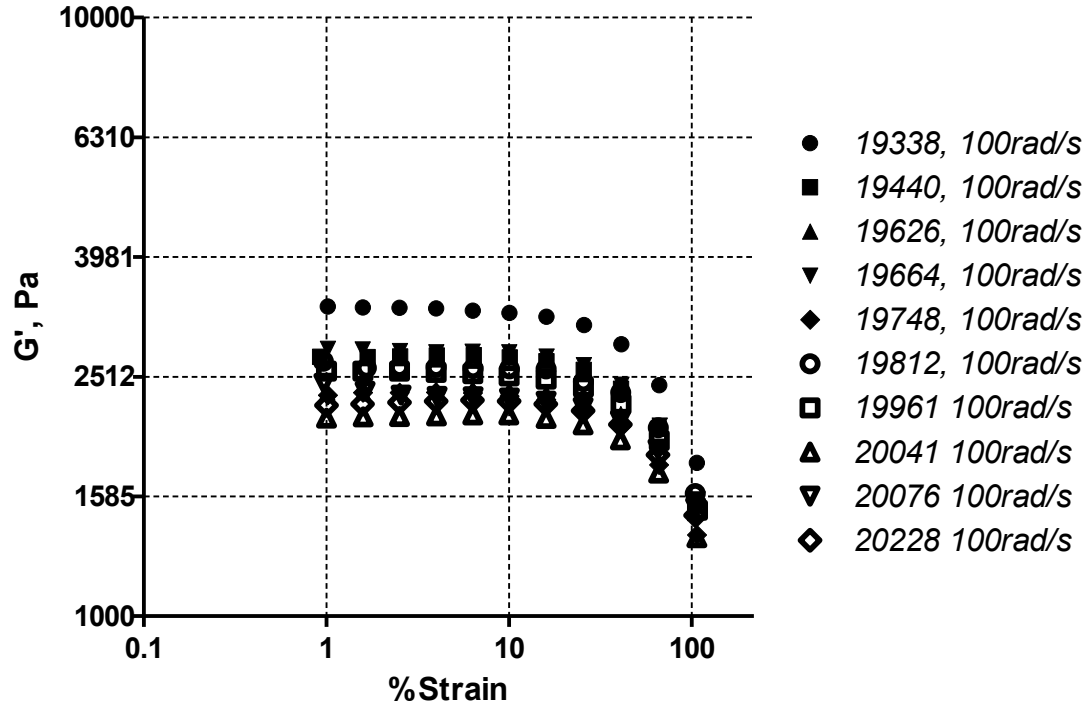


Figure 62. The strain sweep result at 100 rad/s for sodium alginate solutions (ten batches of LF120M at 8% w/w and 37 °C).

APPENDIX II. Sodium Alginate Used in Matrix Tablets

The linear portion of the out-of-die Heckel plot was determined by the 1st derivative method. The 1st derivative values in the compression pressure range from 25 to 265 MPa are listed in Table 30.

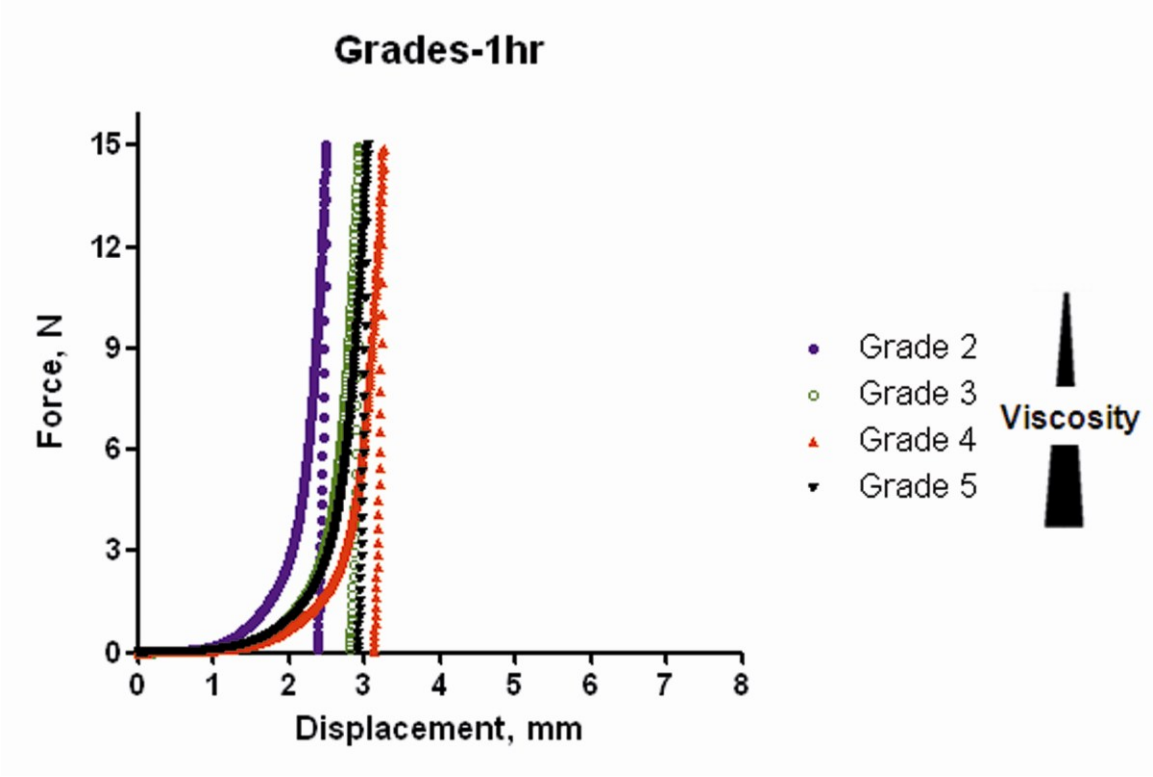
Table 30. The 1st derivative of Heckel plot for the four grades of sodium alginate (Chapter 3).

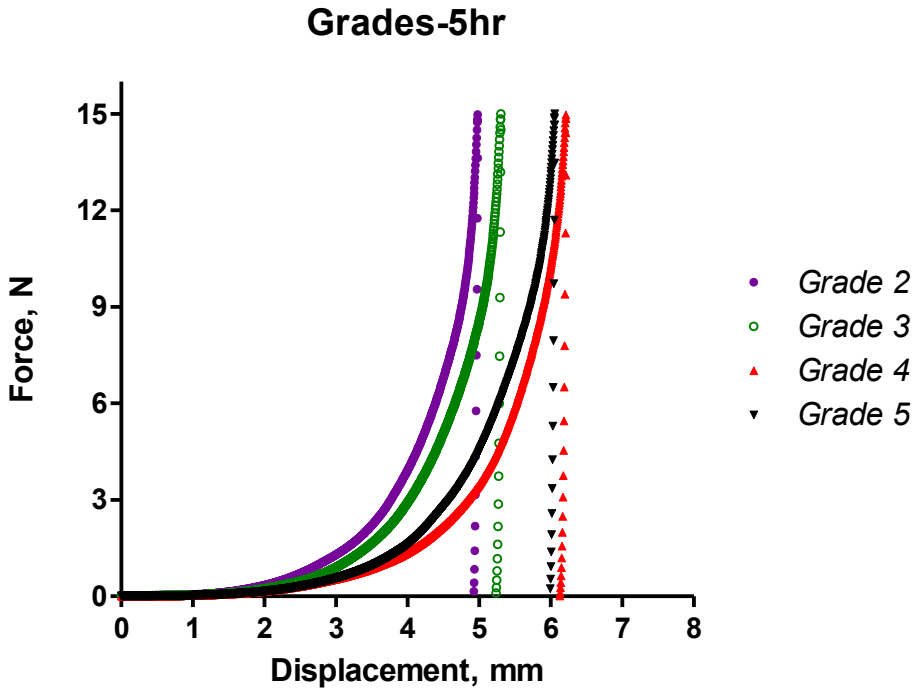
Pressure, MPa	1st derivative of Heckel Plot $\Delta(-\ln\varepsilon)/\Delta P$					
	Grade 2	Grade 3	Grade 4	Grade 5	MCC	Lactose

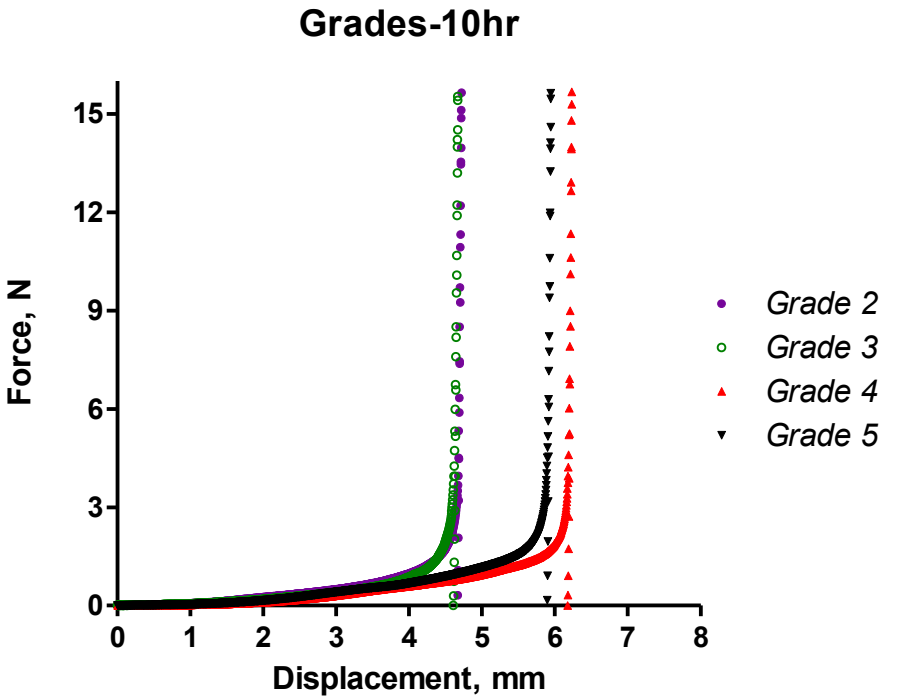
25-50	0.0126	0.0117	0.0113	0.0115	0.0125	0.0078
50-75	0.0064	0.0059	0.0086	0.0060	0.0108	0.0058
75-100	0.0034	0.0041	0.0032	0.0042	0.0097	0.0050
100-125	0.0071	0.0044	0.0056	0.0045	0.0082	0.0051
125-150	0.0043	0.0049	0.0046	0.0050	0.0071	0.0052
150-200	0.0004	0.0003	0.0013	-0.0007	0.0038	0.0022
200-265	0.0003	-0.0001	0.0006	0.0024	0.0027	0.0035

The 1st derivative values of the Heckel plot for various grades, MCC, and lactose anhydrous are in a relatively narrow range from 50 to 150 MPa. With compression pressure increasing from 25 to 50 MPa, there is a relatively high degree of decrease in porosity compacts, which could be due to particle rearrangement and/or fragmentation. On the other hand, with compression pressures higher than 150 MPa, there is a relatively low degree of decrease in porosity of the compacts, which indicates that there is more elastic deformation under high pressure than under low pressure. Thus, data collected from 50 to 150 MPa were used to fit Heckel plot.

The force-displacement profiles for the swelling sodium alginate tablets of four grades and three batches at different time points are depicted in Figure 63 and 64, respectively.


Grades-1hr
Force, N
Displacement, mm
Grade 2
Grade 3
Grade 4
Grade 5
Viscosity


Grades-5hr
Force, N
Displacement, mm
Grade 2
Grade 3
Grade 4
Grade 5


Grades-10hr
Force, N
Displacement, mm
Grade 2
Grade 3
Grade 4
Grade 5

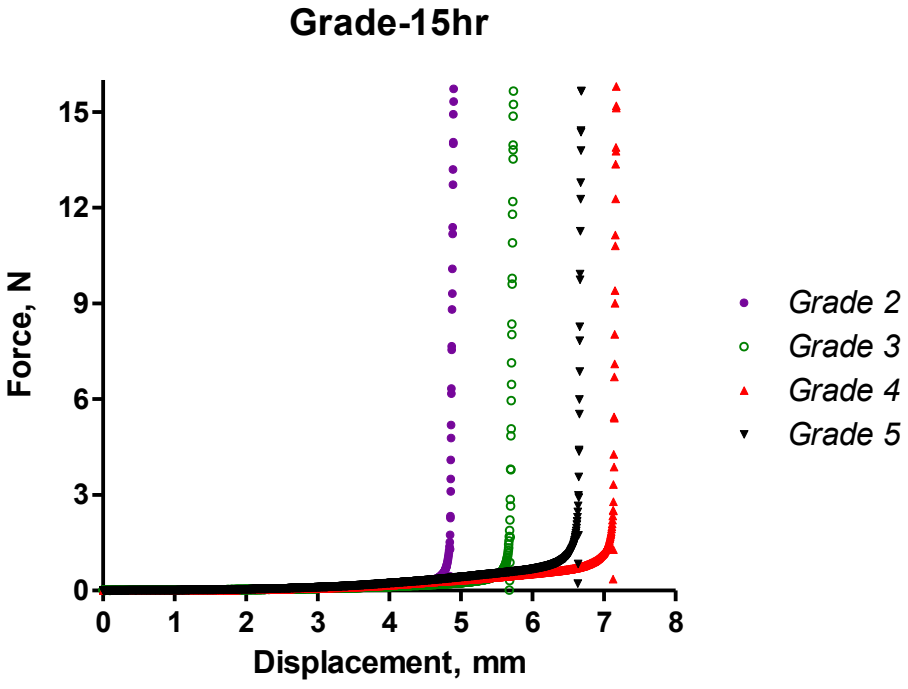
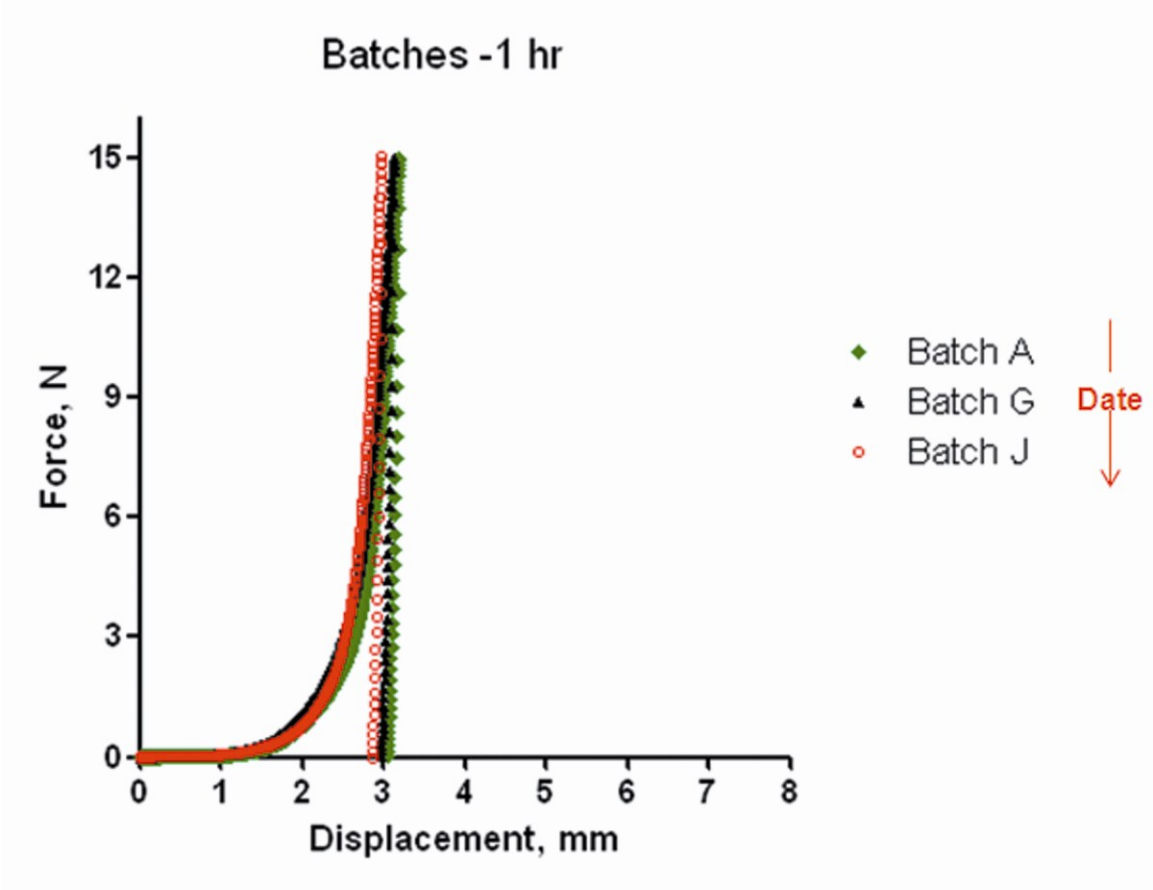
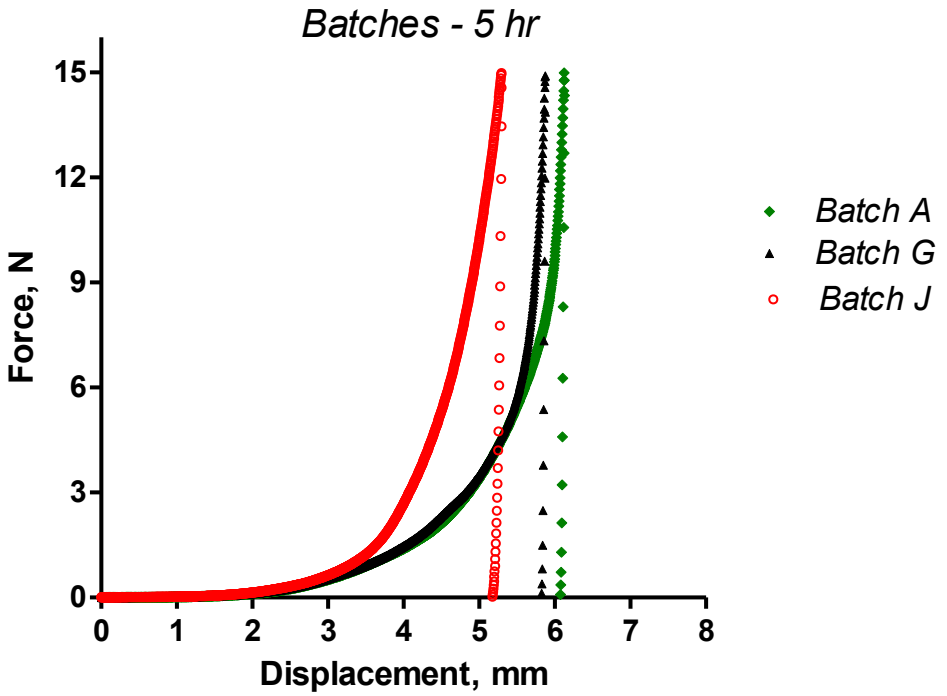
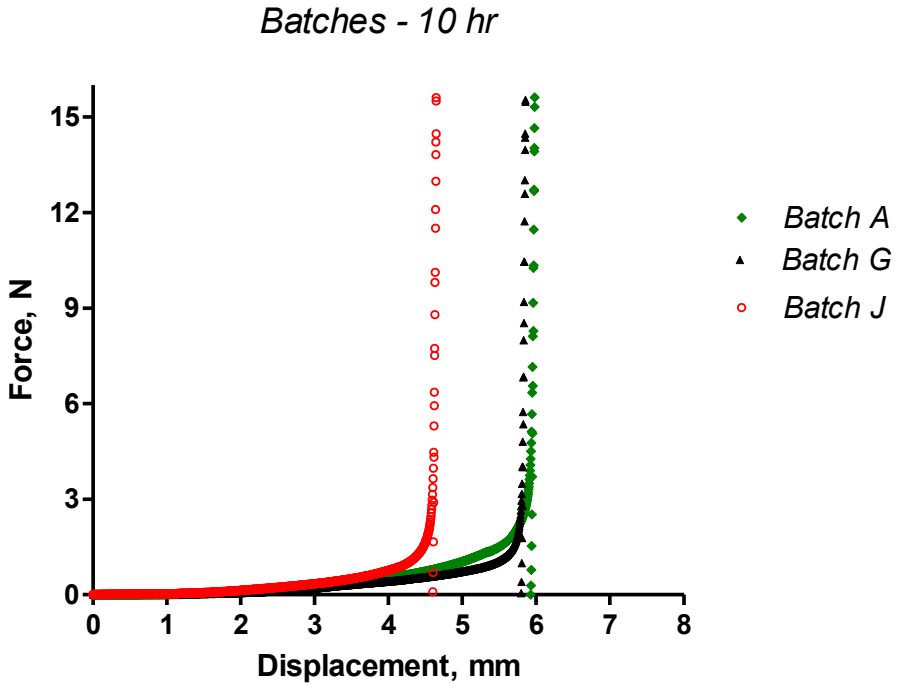

Grade-15hr
Force, N
Displacement, mm
Grade 2
Grade 3
Grade 4
Grade 5

Figure 63. The force-displacement profiles of swollen sodium alginate matrix tablets prepared from four different grades at various time points (1, 5, 10, and 15 h).




Batches - 5 hr
Force, N
Displacement, mm
Batch A
Batch G
Batch J


Batches - 10 hr
Force, N
Displacement, mm
Batch A
Batch G
Batch J

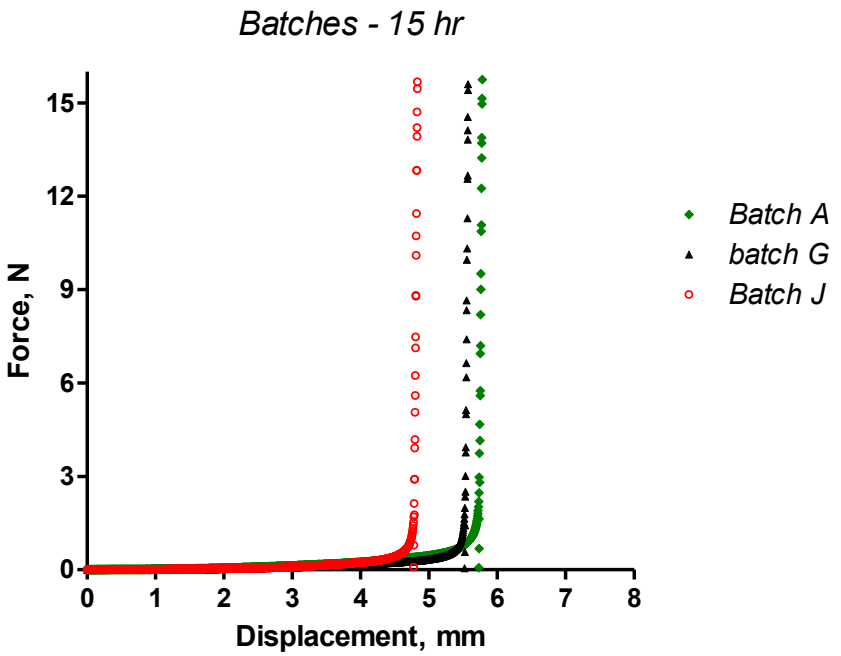


Figure 64. The force-displacement profiles of swollen sodium alginate matrix tablets prepared from three different batches at various time points (1, 5, 10, and 15 h).