CHAPTER 6

Preliminary Investigation and Characterisation of a Gel-Forming Suspending Agent for Extemporaneous Dispensing

6.1. Introduction

At the outset, this chapter sought to investigate various extemporaneous hydrophilic polymeric gels demonstrating system suitability for extemporaneous dispensing. A preliminary screening was conducted in order to identify appropriate suspending and gel-forming agent/s with adequate water dispersibility and viscosity-building characteristics. Use of two or more synergistic agents would allow for a reduction in the bulk quantity of powder required to produce an acceptable suspension than use of a single suspending agent. Preliminary screening, as described, identified the synergism demonstrated in a soluble starch-carrageenan system as being the most apt for the purposes of this investigation.

Starch is one of the most important food hydrocolloids and is often employed as a thickener, gelling agent and stabiliser. Sodium starch glycolate (SSG), a semi-synthetic polysaccharide derivative introduced in Chapter 2, is manufactured by cross-linking and carboxymethylating potato starch. SSG is largely composed of the branched polysaccharides, amylopectin, and the linear polysaccharide, amylose. Its chains have been forced apart by the introduction of bulky sodium carboxymethyl substituents, to render both components more cold water-soluble.

The inclusion of SSG in an extemporaneous granule preparation is warranted owing to its multifunctional nature. As a starch, it possesses weak binding tendencies, and is also claimed to be a significantly better disintegrant than normal starches, exerting its ‘super-disintegrant’ effect via capillary action, as well as demonstrating superiority to other disintegrants such as sodium

carboxymethylcellulose. Previous studies have all reported on the merits of the use of SSG as an extemporaneous suspending agent for a range of pharmaceutical suspensions (Farley and Lund, 1976; Danckwerts et al., 2003). SSG absorbs water rapidly, gelling on prolonged exposure to water, and settles in the form of a highly hydrated layer. At a concentration of 2%$^{w}/_{v}$ sodium starch glycolate disperses in cold water, having a viscosity of 4.26 mPa.s (aqueous dispersion). It is, however, used in concentrations of up to 6.0%$^{w}/_{v}$ in order to achieve optimal functionality in the preparation of pharmaceutical suspensions (Reynolds, 1996). Therefore, a fairly high concentration of the hydrophilic polymer would be required in order to achieve optimum suspension functionality in the dispersible multiparticulate system to adequately suspend the particles. In order to aid viscosity-building and maintain suspension functionality, SSG needs to be used in combination with another gel-forming polymer with which it is preferably synergistic.

It has been demonstrated that the addition of non-starch hydrocolloids to starch systems serves to control rheological and textural properties. The moisture retention and the overall product quality during storage of the system is also improved and maintained. In general, the addition of polysaccharide gums such as xanthan, guar gum, and carrageenan to a starch-based system causes an increase in the viscosity and a decrease in the retrogradation rate. This has been attributed to various molecular interactions between starch and non-starch polysaccharides, namely: the thermodynamic incompatibility between coexisting molecules, the interference of ungelling polysaccharide on the association of the coexisting gelling one, the exclusion effect of swollen granules, and the coupling action between unlike polysaccharide molecules (Chaudemanche and Budtova, 2005).

As discussed, polymer gels are created from polymer networks and solvents. The polymer network envelopes or holds a large amount of liquid and prevents it from flowing out. Many of

these gels undergo a process of reversible gelation upon cooling known as a sol–gel phase transition. Several natural polymer gels fall into the class of physical gels, among which red algae has attracted attention for various applications. Red algae produce a wide range of galactose-based polysaccharides, one of which – carrageenan - has achieved great interest because of its applications in food and other industries (Kara et al., 2003).

Carrageenan is a collective term for high molecular weight hydrocolloid polysaccharides obtained by alkaline extraction (and modification) from some members of the class *Rhodophyceae* (red seaweed). Carrageenan consists of alternating 3-linked-β-galactopyranose and 4-linked-α-galactopyranose units, both sulphated and non-sulphated. Carrageenans are linear polymers of about 25000 galactose derivatives with a structure that is difficult to precisely define. They have demonstrated functionality as suspending agents and will thicken, suspend and stabilise particulates as well as colloidal dispersions and *w/o* emulsions (Valenta and Schultz, 2004). All carrageenans are highly flexible molecules, which wind around each other to form double-helical zones. Their functionality as suspending and gelling agents is a result of a thermoreversible gelation involving a coil-to-helix conformational transition on cooling from a solution heated above 80ºC, often in the presence of gel-inducing and gel-strengthening cations, respectively (Michel et al., 1997).

There are three basic types of carrageenan: iota-, kappa-, and lambda-carrageenan. This investigation focussed on kappa-carrageenan (κC), a strongly gelling polymer, containing 25% ester sulphate by weight and approximately 34% 3,6-anhydrogalactose, having a molecular weight of 415000g/mol. κC is produced by alkaline elimination from μ-carrageenan isolated typically from the tropical seaweed *Kappaphycus alvarezii* (also known as *Eucheuma cottonii*). κC contains one sulphate group for every monomer and their polyanionic nature results in salts

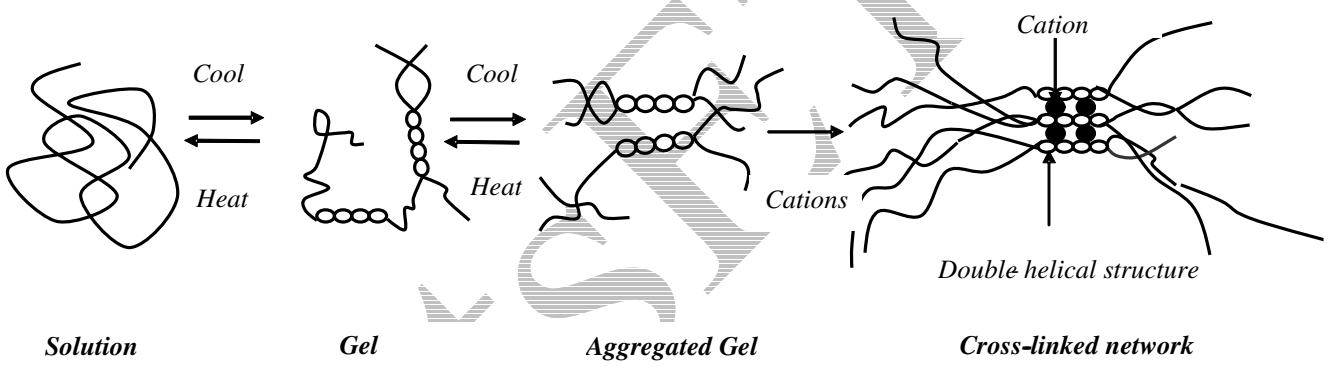
affecting their conformational transitions (Kara et al., 2003). The experimental charge/dimer is 1.03 rather than 1.0, with 0.82 molecules of anhydrogalactose rather than one. In the case of κC, alkaline ions bind to the helix of the hydrocolloid, partially neutralising the sulphate groups. This gives rise to aggregation of the double helices with an increase in gel rigidity (Montero and Perez-Matoes, 2002). The behaviour of low-charged κC is very sensitive to the presence of monovalent ions (Michel et al., 1997).

For a polyelectrolyte gel such as carrageenan the interconnected gel network is a multicomponent system where the nature of counterions and added electrolytes, as well as the interaction of these species with the polymer chains making up the network, regulate the gel structure and its properties (Kara et al., 2003). Gel formation will take place only within a limited composition interval of this medium (Hugerth et al., 1999). Figure 6.1 is a schematic representation of the gelling mechanism for κC. The κC exists either in the coil or helix confirmation and can undergo a thermal as well as salt-induced helix-coil transformation. This order-disorder transition of κC i.e. helix-helix aggregation is responsible for gel formation (Naim et al., 2004). The essential features of the κC system identified thus far are as follows (Hugerth et al., 1999):

1. An ordered, helical conformation is required for aggregation and gelation to occur, promoted by addition of an appropriate electrolyte to a sufficient ionic strength and/or by lowering the temperature.
2. The type of counter- and co-ions present has a profound influence on the κC conformation and aggregation behaviour. In terms of their promoting efficiency for helix formation and helix-helix association in an aqueous environment, the monovalent counterions can be divided into two main categories, i.e. 'non-specific' counterions (Li^+, Na^+, and $(CH_3)_4N^+$) and 'specific' counterions (NH_4^+, K^+, Cs^+ and Rb^+). The former act primarily by long-range Coulombic forces whereas the latter bind specifically to the carrageenan chain

neutralising the Coulomb repulsion force between the polymer chains in the cross-link point (Hugerth et al., 1999; Kara et al., 2003). These ions have the capacity to induce helix conformation and promote helix-helix aggregation, thereby facilitating gel formation (Hermansson et al., 1991; Michel et al., 1997).

Due to the strong specific interaction between the cations and κC, as their levels increase, the structure becomes tightly aggregated, exhibiting an increase in gel strength (Naim et al., 2004). The stronger the interaction between the cation and carrageenan, the more heterogenous is the phase formed. These interactions significantly affect the consistency or texture of the κC gel



(Keogh et al., 1995).

Figure 6.1: Gel formation in carrageenan

The consequential outcome is a three-dimensional gel-type network (Figure 6.1), which provides excellent suspension functionality. They also acquiesce a thixotropic character, yielding a pourable liquid at fairly low use levels that reforms a gel for long-term stability of, for example, pharmaceutical suspensions (FMC Biopolymer: Carrageenan Technical Data Sheet, 2005).

The advantages of starch-carrageenan gel systems have been demonstrated in numerous applications and exploitation of the synergism between starches and carrageenan could see the

formation of a supporting aggregated network and an improvement in the textural properties of a pharmaceutical gel-forming suspension prepared by employing a combination of the two polymers rather than use of either one alone (Hegenbart, 1991). Carrageenan is increasingly being employed in food products to improve their texture and, when used in combination with starch, which imparts body and mouthfeel to the product, highly desirable textural attributes can be realised (Verbeken et al., 2004). In addition to its textural benefits, starch-carrageenan gel systems offer resistance to shear degradation; starches slow the eventual settling through viscosity-building, and carrageenan maintains stability for longer periods because of the three-dimensional gel networks it forms following gelation under the specified conditions (Van de Velde et al., 2005).

Previous studies, in recognition of the reported advantages of starch-carrageenan systems, have employed various techniques for characterising the properties of these composite gels. Tecante and Doublier (2002) combined rheological and turbidity measurements to investigate the interaction within and viscoelastic properties of amylose-κC mixtures. They deduced that addition of relatively small amounts of carrageenan accelerated amylose gelation to a certain extent, beyond which further addition retarded gelation and affected the rigidity of the resulting mixture. These effects occurred in the presence or absence of KCl, however, its presence conferred higher gel rigidity. Tecante and Doublier (1999) also reported on the differing shear behaviours of varying mixtures of cross-linked waxy corn starch (CWCS), κC and KCl. The combination of CWCS with carrageenan and KCl resulted in mixtures possessing different rheological behaviours. Lai, Huang and Lii (1999) investigated the changes in rheological properties and gelling, and gel-melting temperatures of κC by the addition of various starch systems. Gelation of κC was accelerated by the addition of starches, possibly due to coupling actions between κC and soluble starch molecules.

The gel properties of κC-starch composites are purported to be governed by the exclusion effect of swollen starch granules, resulting in higher carrageenan concentrations in the continuous water phase (Keogh et al., 1995; Montero and Perez-Matoes, 2002). The interaction between these starch and κC macromolecules is what is alleged to determine the final texture and functional properties of gel admixtures, making the study of their textural properties of interest. It is yet to be ascertained whether this synergism is evident in starch-carrageenan sol systems. Modified starches, such as SSG, possess important industrial applications; however, the literature on their performance, either alone or in combination with hydrocolloid components, is less abundant. In addition to the reported thermodynamic incompatibilities of the composite polysaccharide systems, interaction between the ionic components of the modified starch and carrageenan may facilitate reversible cross-link and gel formation.

In order to obtain a better understanding of the interactions between the starch and hydrocolloid of interest, characterisation of the composite systems can be achieved through evaluation of their mechanical properties, provided they exhibit a moderate cross-linking degree (Odian, 1991). The molecular interactions between polysaccharide molecules are frequently investigated using rheological methods (Chaudemanche and Budtova, 2005). Here force-displacement testing was employed for the mechanical characterisation of the composite systems.

Identification of a candidate gel-forming SSG-κC system prompted investigative validation of composite system suitability; innovatively demonstrated by characterisation of the mechanical/ textural properties, and viscosity transitions in κC systems and SSG-κC systems prepared under ambient conditions or conditions promoting thermal gelation. This was achieved through analysis of the textural profiles following force-displacement testing, and through viscometry, to ascertain whether increasing κC concentrations significantly improved these properties. In particular, the

ability of SSG-κC systems to form an aggregated supporting gel-forming network with improved mechanical properties in the absence of thermally-induced gelation of κC was of importance in the formulation of an extemporaneous suspension system.

6.2. Preliminary Evaluation of Appropriate Suspending and Gelling Agents for Extemporaneous Dispensing

6.2.1 Materials and Methods

6.2.1.1. Materials

Sodium starch glycolate, SSG, was obtained from Betabs Pharmaceuticals (Pty) Ltd (Johannesburg, South Africa). Carrageenan commercial grade Type 1 (predominantly κ-carrageenan and lesser amounts of λ-carrageenan) and xanthan gum were purchased from Sigma-Aldrich (St. Louis, USA). Carboxymethylcellulose (sodium salt) and polyvinylpyrrolidone were obtained from BDH® (BDH Chemicals Ltd and BDH Laboratory Reagents, Poole, UK). Tragacanth gum was purchased from Unilab (Saarchem, Krugersdorp, South Africa).

6.2.1.2. Preliminary Suspension Preparation and Evaluation

In addition to the soluble starch derivative, SSG, the ease of preparation and dispersion in tepid water and the final viscosity of the following hydrophilic polymeric gelling agents cited for extemporaneous use were compared: sodium carboxymethylcellulose, a semi-synthetic polysaccharide derivative; tragacanth gum, an easily dispersible widely used suspending agent for extemporaneous use; xanthan gum, which is soluble in cold water and has been found to be easier to use and capable of preparing suspensions of better quality and improved consistency compared with tragacanth; carrageenan, a red algal polyelectrolyte derivative; and polyvinylpyrrolidone, a linear polysaccharide of 1-vinylpyrrolidone (Reynolds, 1996).

0.5%$^{w}/_{v}$ suspensions of each agent were prepared by slow addition of the powdered agent to 500mL tepid double-deionised water (Milli-Q System, Millipore, Bedford MA, USA) under moderate agitation (500rpm) for 15 minutes using a two-blade propeller stirrer (Heidolph®, Labotec, Gauteng, South Africa) at 20°C. Suspensions were prepared in triplicate. A Brookfield Digital Viscometer (Model DV-II+, Spindle RV1, Speed 1-50rpm) was employed to measure the final viscosity of the various suspensions tested (expressed as mean±SD of five measurements), which would influence the ability of the enterospheres and RIF to be suspended with minimal sedimentation before administering the suspension, in accordance with Stoke's Law.

6.2.2. Results and Discussion

From Table 6.1, the following can be gauged with regard to the extemporaneous performance of the suspending agents. The ease of dispersion of the modified starch, SSG, was optimal for suspension system application, which is required to be dispersed in tepid water immediately prior to administration. Sodium carboxymethylcellulose dispersed with difficulty due to inadequate wetting and lump formation. Carrageenan dispersion was satisfactory and the suspenion demonstrated a fairly high viscosity at a comparatively low use level. Tragacanth gum dispersed fairly readily in tepid water, however, the suspension had a reasonably low viscosity when prepared under the described conditions. Tragacanth is widely used as a suspending agent usually in the form of tragacanth mucilage. Dispersion of tragacanth in water alone has been facilitated by first wetting the gum in ethanol, in which it is completely insoluble (Lund, 1970). Although xanthan gum is purported to be soluble in hot and cold water, dispersion was not readily achieved. After moderate agitation for 20 minutes, a highly viscous gel was obtained. Synergisms reported in Table 6.1 are as described in various works (Grierson, 1992; Nussinovitch, 1997; Cui, 2001).

Table 6.1: Characteristics of hydrophilic suspending agents for extemporaneous dispensing

Suspending Agent at 0.5% $^{w}/_{v}$	Synergism	Ease of Preparation	Viscosity (mPa.s)
Sodium Starch Glycolate (SSG) (Explotab®)	Possible between amylose component and carrageenan, xanthan gum, guar gum, but not clearly elucidated.	Easy. Dispersed with moderate stirring for 1 minute.	2.10±0.0
Sodium Carboxymethylcellulose	Carob gum, yellow mustard gum	Difficult. Dispersed with moderate stirring for 15-20 minutes.	39.30±6.40
Kappa-carrageenan	Starches, proteins (plant and animal origin e.g. milk κ-casein), konjac glucomannan, locust bean gum	Fair Dispersed with moderate stirring for 5 minutes.	95.55±11.27
Tragacanth Gum	Yellow mustard gum (small interaction)	Fair. Dispersed with moderate agitation for 5 minutes.	27.21±2.41
Xanthan Gum	Starches, yellow mustard gum (small interaction), locust bean gum, konjac glucomannan	Difficult. Dispersed with moderate agitation for 20 minutes.	2947.5±753.92
Polyvinylpyrrolidone	ND[a]	Easy. Dispersed with moderate agitation for 5 minutes.	14.53±1.14

[a]*ND=no scientific data demonstrating synergism*

Various authors have demonstrated the synergism of starch-carrageenan composites and the possibility of their combined use to formulate a suspension of optimal functionality is an attractive option (Hegenbart, 1991; Lai, Huang and Lii, 1999; Tecante and Doublier, 1999; Verbeken et al., 2004; Van de Velde et al. 2005). Because both agents dispersed with relative ease in tepid water with carrageenan demonstrating adequate viscosity-building characteristics, ensuing investigations focused on the characterisation of the aforementioned combination.

6.3. Textural Profiling of a Sodium Starch Glycolate-Carrageenan Combination: Demonstration of the Functional Synergism

6.3.1. Materials and Methods

6.3.1.1. Materials

Sodium starch glycolate, SSG, was obtained from Betabs Pharmaceuticals (Pty) Ltd (Johannesburg, South Africa). Carrageenan commercial grade Type 1 (predominantly κ-carrageenan and lesser amounts of the more cold water-soluble λ-carrageenan) was purchased from Sigma-Aldrich (St. Louis, USA). Additional reagents were all of analytical grade and were purchased from Rochelle Chemicals (Johannesburg, South Africa).

6.3.1.2. Preparation of SSG-κC Sol and Gel Systems

The textural and viscosity behaviour of SSG suspensions at low use levels (1-6%$^{w}/_{v}$) was unremarkable. Therefore, in order to obtain significant information on the interactions present in SSG-κC composite systems, κC and SSG-κC were prepared under the following conditions: (i) heating followed by quenching promoting thermally-induced gelation ('gel' systems), and (ii) ambient conditions ('sol' systems). κC sol and gel systems were prepared incorporating increasing concentrations of κC at typical use levels (0.0% $^{w}/_{v}$, 0.1% $^{w}/_{v}$, 0.5% $^{w}/_{v}$, and 1.0% $^{w}/_{v}$). Composite systems were formulated, keeping the concentration of the SSG constant (2.0% $^{w}/_{v}$) and incorporating increasing concentrations of κC (0.0% $^{w}/_{v}$, 0.1% $^{w}/_{v}$, 0.5% $^{w}/_{v}$, and 1.0% $^{w}/_{v}$). Sol systems were prepared following dispersal of SSG and/or κC in double-deionised water under mechanical stirring. The resultant gel systems were obtained as described for the sol systems followed by heating at a rate of 10°C/min to 80°C in a water bath and maintaining the systems at the designated temperature (80°C) for 5 minutes to achieve complete dissolution of κC. The hot solutions were then quenched at a moderately rapid rate (2.5°C/min) to room temperature to form a gel.

6.3.1.3. Textural Analysis of Sol and Gel Systems

Compression tests were performed on 1mL samples of the various disperse and thermally-gelled systems using a TA.XT.*plus* Texture Analyser (Stable Micro Systems, Surrey, UK) fitted with a 60^{o} conical Perspex® probe (Figure 6.2) under the conditions shown in Table 6.2 employing double-deionised water as a blank. All tests were performed in triplicate (n=3).

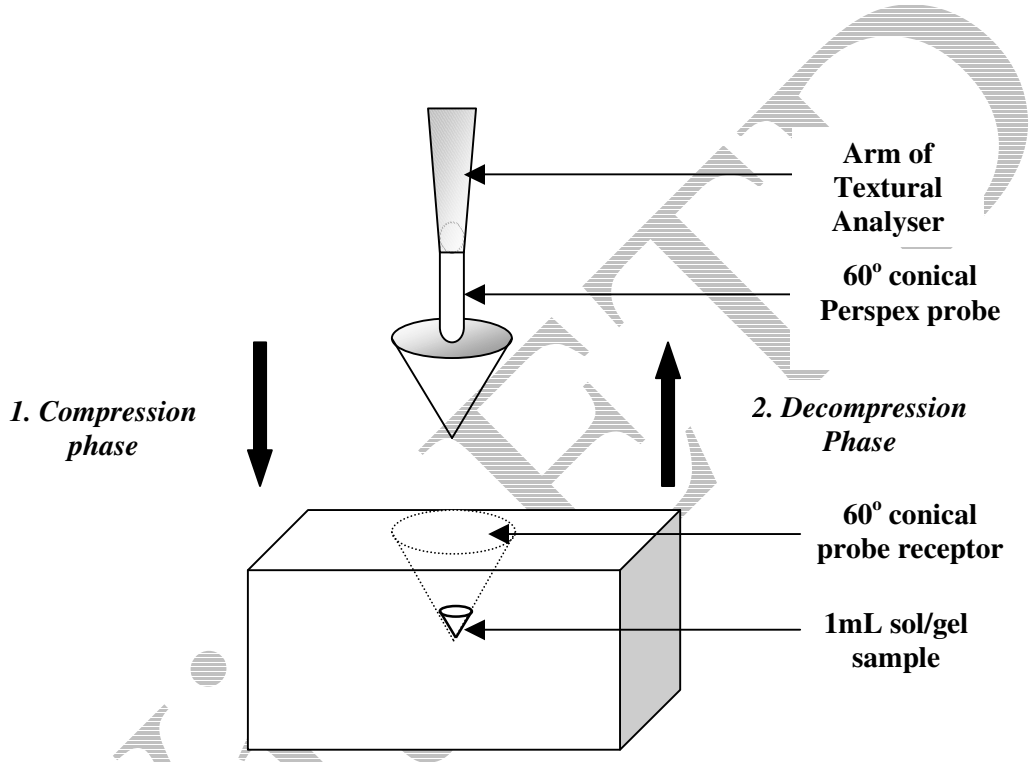


Figure 6.2: Conical probe configuration illustrating the compression and decompression phases

Table 6.2: TA-XT.plus settings for sol and gel analysis

Parameters	Settings
Probe	60^{o} conical Perspex probe
Pre-Test Speed	1.00 mm/second
Test Speed	0.50 mm/second
Post-Test Speed	1.00 mm/second
Test Mode	Compression
Force	40.00 N
Hold Time	20.00 seconds

6.3.1.4. Gelation and Viscosity Analysis of Sol and Gel Systems

A Brookfield Digital Viscometer Model DV-II+, Spindle No. 4, Speed: 0.5-50 rpm (Brookfield Engineering Laboratories, Inc., Stoughton, Massachusetts, USA) was used to measure the viscosity of sol systems and monitor the change in viscosity (rate of gel formation) of the gel systems (equilibrated at 80°C) as they cooled at a rate of 2.5°C/min to room temperature, employing double-deionised water as a blank for comparison. Readings were recorded at 5-minute intervals over 25 minutes, at which time the final viscosity (V_{t25}) was calculated and recorded.

6.3.1.5. Statistical Analysis

The effects of an increasing κC concentration on the mechanically-derived textural properties (compressibility and adhesivity), and final viscosity of the systems were statistically compared using a one-way ANOVA (Minitab® Statistical Software, V14, Minitab, USA). A 95% confidence interval was used in all cases.

6.3.2. Results and Discussion

6.3.2.1. Selection of Processing Conditions for Gel Systems

Preliminary investigations confirmed that phase separation of mixed biopolymer systems, their final structure and textural properties were strongly dependent on processing temperature and times and cooling rates. During gel formation, these factors affected the dynamic process of competition between phase separation and gel formation (Nunes et al., 2004). When the gel systems were initially subjected to low quenching rates (0.5°C/min), two distinct gel layers formed. Heating of the systems with rapid cooling yielded the most reproducible results with gels exhibiting less phase separation ascribed to promotion of formation of junction areas with a more

even distribution of starch aggregates. The prepared suspensions (100mL) were thus heated at a rate of 10°C/min to 80°C in a water bath and maintained at this temperature for 5 minutes. The resultant gel systems (Table 6.3) were then allowed to cool at a moderately rapid rate (2.5°C/min) to room temperature prior to testing.

6.3.2.2. Formation of a Three-Dimensional Network in SSG-κC Sol and Gel Systems

The thermoreversible gelation of the carrageenan polyelectrolyte involves a coil-to-helix transition upon cooling followed by aggregation of the ordered molecules to form an infinite network (Koutsoukos, 2002). As expected for polyelectrolytes, the counterion plays an important role in the gelation process and in this work it is postulated that a weak gelation of κC could be induced even in the absence of a quenching phase. With reference to their viscoelastic behaviour, the gelling ability of carrageenans, especially κC, is influenced by alkali treatment, as deesterification of the sulphate groups results in enhanced tendency to form gels in aqueous solutions. By the formation of the 3,6-anhydro bond, the solubility in water is decreased. Moreover, sulphate groups hinder the formation of single and double helices, due to their bulky nature and electrostatic repulsion. By deesterification, the helices are stabilised by hydrogen bonds. Not only is the modulus increased by alkali treatment, but also the temperature at which the modulus decreases rapidly is higher after treatment. Alkali metal cations are thus able to increase the gelation tendencies of κC. The cation dependence of the gel modulus follows the Hofmeister series: $Cs^+ > Rb^+ > K^+ >> Na^+ > Li^+$ - this is in agreement with statements made on the dependence of the cross-link structure on the alkali metal ions (te Nijenhuis, 1997).

As non-specific counterions for κC, Na^+ promotes helix formation in an aqueous environment, acting primarily by long-range Coulombic forces. Recently, Ramakrishnan and Prud'homme (2000) have demonstrated that Coulombic interactions dominated the mechanism of gelation

(Koutsoukos, 2002). The stoichiometric ratio in which the hydrogen sulphate anions of κC and Na^+ interact would have a determining role in whether gelation, aggregation and phase separation occurred. The long-range co-ordination of a Na^+ cation to sulphate groups on two different helices would lead to sets of cation-sulphate-cation interactions, which are not necessarily continuous, owing to their non-specific nature (Arnott et al., 1974). Na^+ thus participates in an aggregation process to form weak gels with κC.

In the case of the investigated systems, where the formation of double helical molecular structures was promoted (i.e. thermally-induced), subsequent aggregating cross-linkages resulted in junction zones as visualised in Figure 6.1. In the absence of thermal induction, the networks of κC were formed through physical aggregation, predominantly disordered but with regions of local order. The consequential outcome was a three-dimensional gel or gel-type network, which is purported to provide excellent suspension functionality. Proposed molecular interactions between the system components are demonstrated in Figure 6.3. The three-dimensional nature of the networks formed in SSG-κC systems is microscopically demonstrated in Figure 6.4. In accordance with the classifications provided by te Nijenhuis (1997) on the microscopic appearance of the network, a phase connected (adhesive) morphology was observed. The more pronounced exclusion effect at the higher κC concentrations was noted (Figure 6.4(b)).

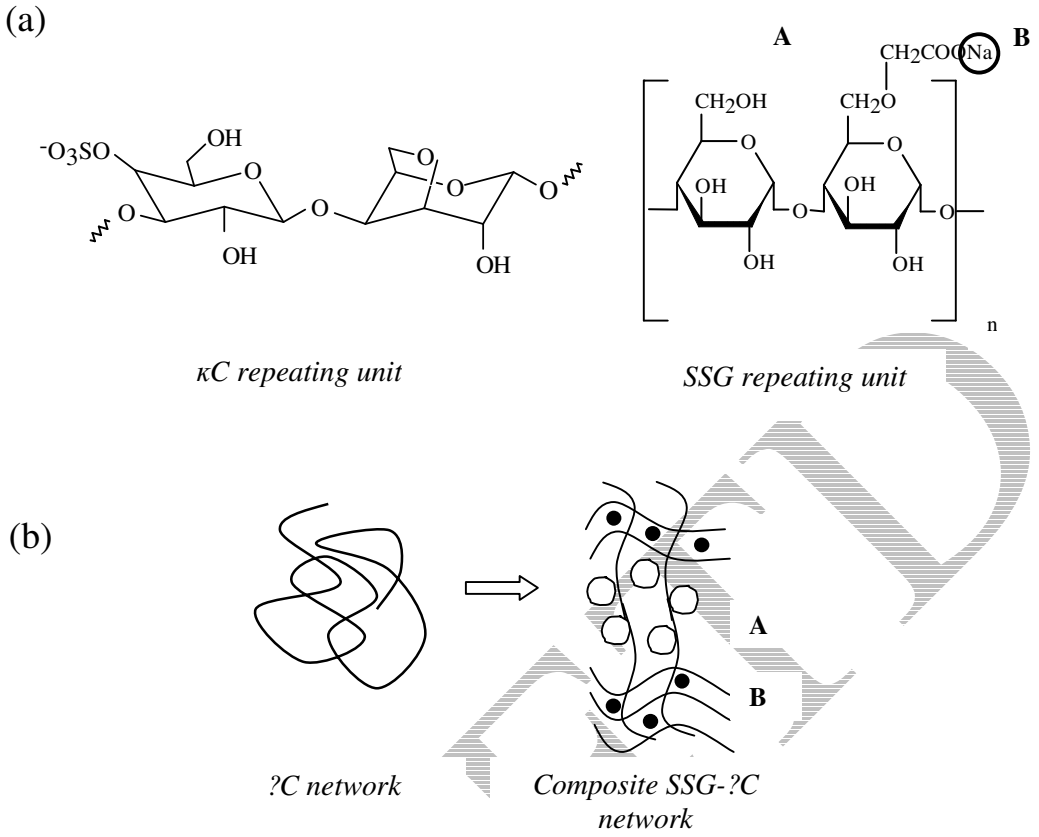


Figure 6.3: (a) Structural formulae of SSG and κC repeating units and (b) schematic of proposed effect of SSG on κC due to (A) exclusion effects (B) Coulombic interactions

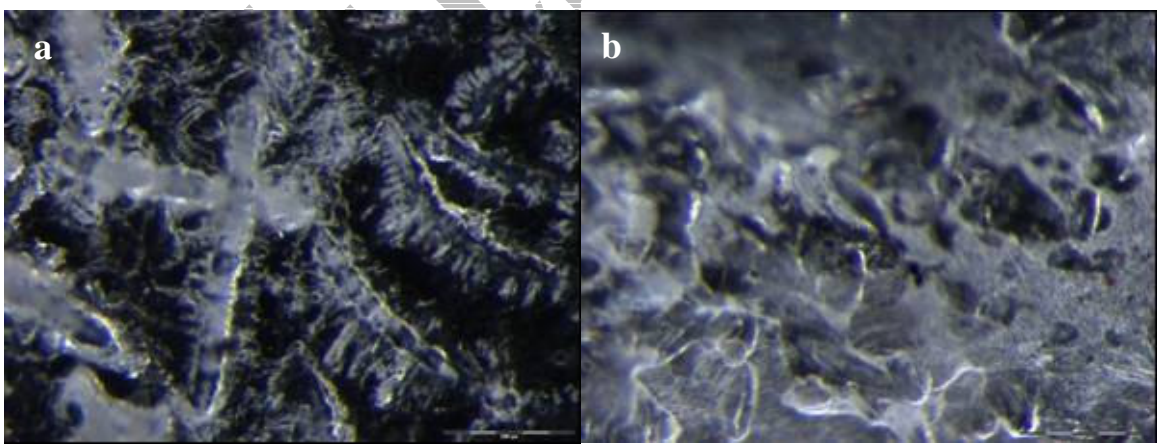


Figure 6.4: Stereomicrographs (darkfield; 100x magnification, scale bar=200µm) of SSG-κC sol systems: (a) 0.5%$^{w}/_{v}$ κC and (b) 1.0%$^{w}/_{v}$ κC

6.3.2.3. Textural Analysis of Sol and Gel Systems

The textural profiles depicting the positive and negative areas (AUC) under the force-distance plots representative of the work performed (in Joules) are shown in Figure 6.5. From the resultant force-displacement plots, the following parameters were derived:

1. Compressibility (the work required to deform the system during the compression phase of the probe). It was recorded as the positive area of the force-distance plot of the compression phase.
2. Adhesivity (the work required to overcome the attractive forces between the surface of the sample and the surface of the probe during the decompression phase). It was recorded as the negative area of the force-distance plot of the decompression phase, which serves as a good index of the adhesivity of the systems (Jones et al., 2004).

The compressibility was instituted as a measure of the stress-strain behaviour of the composite systems as described by Odian (1991). It was proposed that the greater the degree of interaction in the SSG-κC system, the more work that would be required to overcome the attractive forces for deformation of the system, and the greater the calculated compressibility. Figure 6.6 provides graphical representation of the effects of increasing levels of κC on system compressibility.

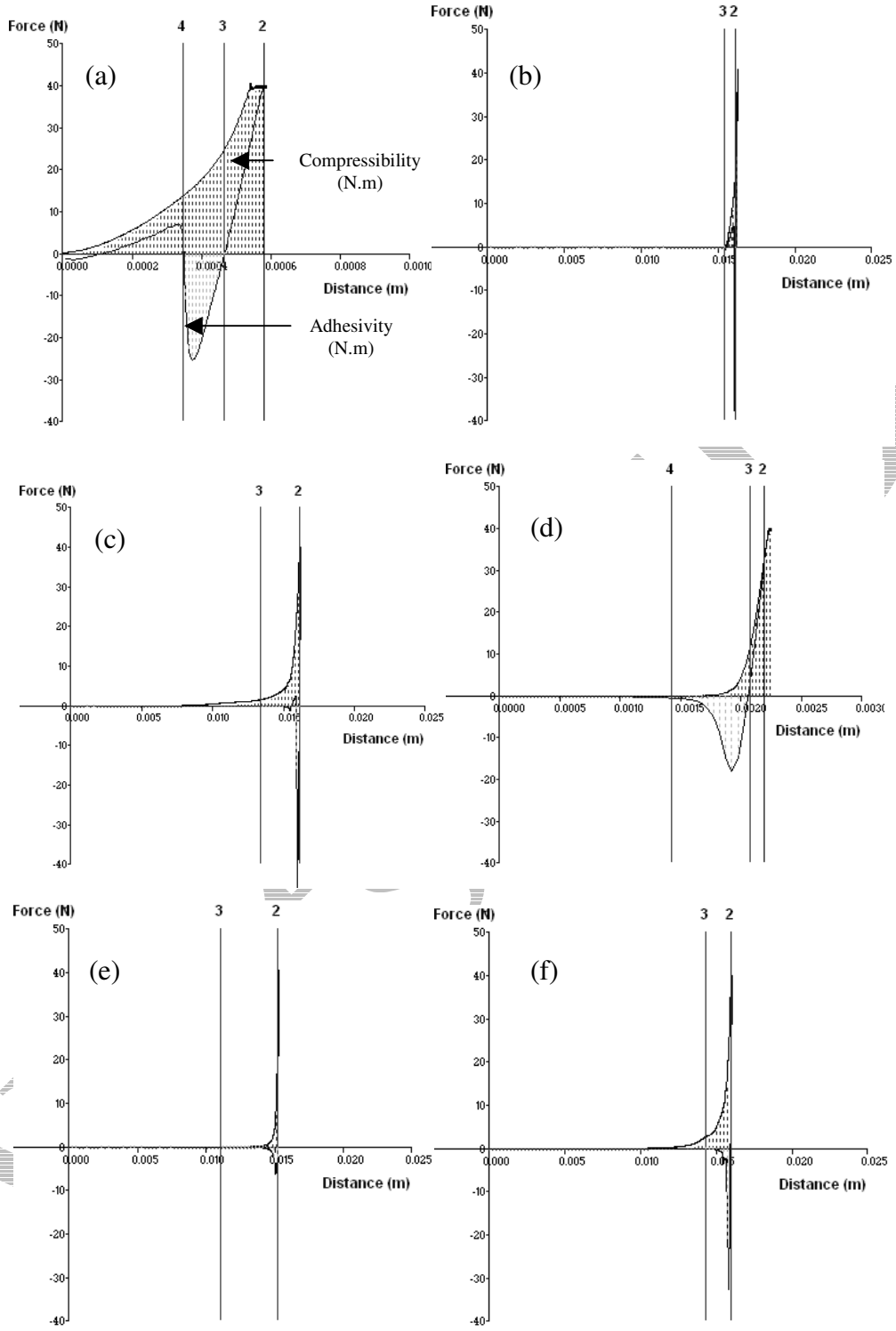


Figure 6.5: Representative textural profiles depicting the AUC: (a) System 1 (2%$^{w}/_{v}$ SSG sol) (b) System 7 (1%$^{w}/_{v}$ κC sol) (c) System 14 (1%$^{w}/_{v}$ κC gel) (d) System 2 (2%$^{w}/_{v}$ SSG 0.1%$^{w}/_{v}$ κC sol) (e) System 4 (2%$^{w}/_{v}$ SSG 1%$^{w}/_{v}$ κC sol) (f) System 11 (2%$^{w}/_{v}$ SSG 1%$^{w}/_{v}$ κC gel)

Table 6.3 represents the results of textural and viscosity analysis of the SSG-κC systems. Results are expressed as the mean±S.D. of three experiments (n=3).

Table 6.3: Textural properties and viscosity of SSG-κC systems

SSG-κC System	Sol/Gel	SSG (%$^{w}/_{v}$)	κC (%$^{w}/_{v}$)	Compressibility (N.m=J) (x10^{-3})	Adhesivity (N.m=J) (x10^{-3})	V_{t25} (mPa.s)
1	Sol	2.0	0	28.79±0.70	1.72±0.12	12.00±0.00
2	Sol	2.0	0.1	100.53±7.99	1.40±0.00	26.00±2.83
3	Sol	2.0	0.5	181.02±77.30	2.03±0.18	132.00±0.00
4	Sol	2.0	1.0	249.48±1.55	1.76±0.31	1656.00±8.00
5	Sol	0	0.1	99.72±5.16	0.24±0.03	17.33±2.31
6	Sol	0	0.5	172.62±4.19	1.00±0.00	97.33±2.31
7	Sol	0	1.0	213.35±59.08	1.55±0.44	145.33±10.07
8	Gel	2.0	0	28.35±0.02	1.65±0.32	12.00±0.00
9	Gel	2.0	0.1	101.25±6.34	1.40±0.00	20.00±0.00
10	Gel	2.0	0.5	235.42±1.48	1.57±0.07	66.67±2.31
11	Gel	2.0	1.0	256.75±9.31	5.50±0.24	3566.00±613.77
12	Gel	0	0.1	98.66±4.10	0.21±0.03	10.00±2.83
13	Gel	0	0.5	188.60±60.31	5.12±0.41	1816.00±137.58
14	Gel	0	1.0	257.24±14.72	5.45±0.12	3785.33±119.49

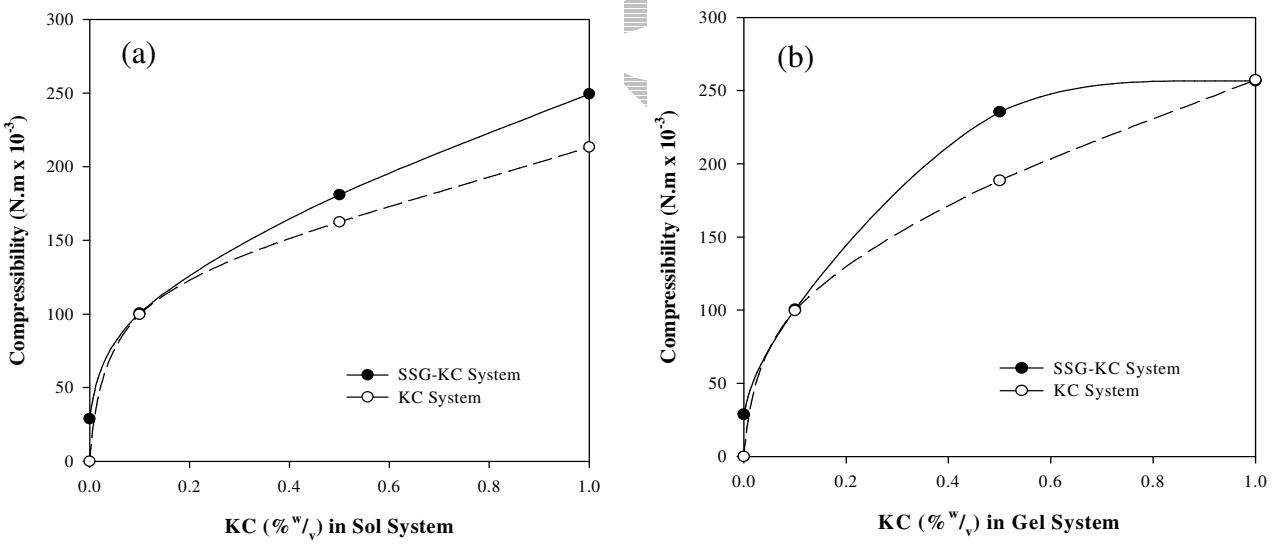


Figure 6.6: Effect of increasing κC concentrations on compressibility: (a) of sol systems 1-7 and (b) of gel systems 8-14

As the amount of κC employed in both the sol and gel κC and SSG-κC systems increased, the compressibility in sol systems (p=0.019) and gel systems (p=0.006), was significantly increased. In κC sol systems 5-7, the compressibility was increased 73.11 to 113.96%. In composite SSG-κC sol systems 1-4, the increase in compressibility was more significant (249.11 to 766.40%). The same trend was observed for gel systems: in κC systems 12-14, the compressibility was increased 89.14% to 157.98%, and the compressibility of SSG-κC systems 8-11 was increased 18060 to 37753%.

In addition to the known synergism promoting gel formation in starch-carrageenan systems, which promoted κC to occupy a greater hydrodynamic volume due to starch exclusion effects, gel formation in the κC phase was enhanced in both sol and gel systems in the presence of monovalent Na^+, which are availed by the sodium carboxymethyl substituent of SSG. More energy was thus expended in deforming the ionically-cross-linked gelled network.

Na^+ promoted helix formation in an aqueous environment by long-range Coulombic forces. This is in contrast with counterions, such as K^+, which bind specifically to the carrageenan chain (Hugerth et al., 2003). The specificity of the interaction between K^+ and κC results in the formation of a more heterogenous phase with an increase in the concentration of the specific ion; whereas the gels formed in the presence of Na^+ exhibited almost no dependence its concentration (Hermansson et al., 1991; Michel et al., 1997). This absence of heterogeneity even in the presence of increased concentrations of Na^+ (when compared to K^+ and Ca^{2+}) allowed for exploitation of this functional synergism at various SSG: κC ratios resulting in the formation of a composite system with favourable textural attributes, and has been reported elsewhere (du Toit et al., 2006).

6.3.2.4.Viscosity Analysis of Sol and Gel Systems

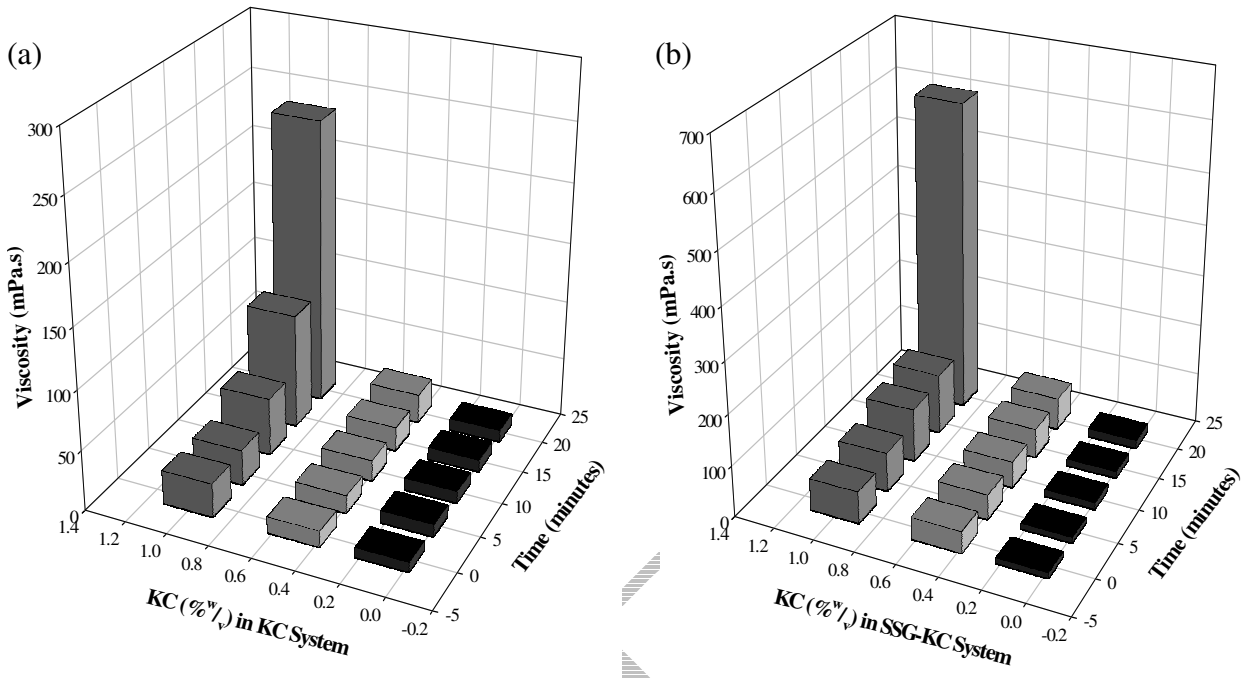


Figure 6.7: Effect of κC levels on the change in viscosity following the sol-gel transition: (a) κC systems 12-14 (b) SSG-κC systems 9-11

SSG-only systems 1 and 8 yielded low viscosity suspensions (0.012±0.000Pa.s) at the concentration employed in the absence of κC. The presence of κC increased the viscosity of composite sol systems (1.17 to 130 times) and gel systems (0.67 to 296.17 times) compared to systems 1 and 8. The effect of κC on the final viscosity of gel systems was significant ($p=0.042$) with rigid gelation of the systems occurring upon cooling when the κC concentration was 1.0%$^{w}/_{v}$. The increase in the viscosity of various starch-hydrocolloid systems and its dependence on the concentration of the hydrocolloid component in the mixture has been demonstrated by several authors (Hermansson et al., 1991; Keogh et al., 1995; Michel et al., 1997) and ascribed to synergism. Tecante and Doublier (1999) established that starch pastes prepared in the presence of hydrocolloids exhibited higher viscosities and normally higher dynamic moduli than starch-alone

preparations. Figure 6.7 represents the change in viscosity of the SSG-κC systems when increasing concentrations of κC were employed.

The hydrocolloid networks produced by interaction with cations are dynamic systems. As described by Luh et al. (1977) in the shrinking core model for the gelling process, the carrageenan hydrocolloid gelling reaction is a function of the reactant cationic agents and its concentration. Following dispersion of the system components in water, no remarkable increase in viscosity was noted after allowing the sol systems to develop for 5 minutes. However, following the application of heat to the SSG-κC composite systems, the κC was solubilised and present as randomly orientated polymeric chains. The gelling process was therefore protracted during the thermally-induced gelation due to the initial requirement of coil-to-helix transitions of κC prior to association with cations to form an aggregated gel network. Further gel strengthening in this case depended on cation diffusion through the κC gel and varied with the time until all available cations had interacted. The cation-hydrocolloid interactions led to a gradual strengthening of the gel, as attested by the slow rise in viscosity in the SSG-κC composite system. For thermally-induced gel systems 8-10, 12, and 13, the increase in viscosity with time was gradual and no distinct gel point was observed. Formation of a solid-like (as opposed to liquid-like) gel and the observation of a gel point was only for systems 11 and 14 following thermally-induced gelation and employment of κC concentrations $\geq 1.0\%^{w}/_{v}$. In this case, the viscoelastic properties changed dramatically: the system was liquid-like before the cross-linking started and remained liquid until the viscosity became infinite. At a distinct moment, called the gel point, there was at least one molecule with an infinite molecular weight (te Nijenhuis, 1997).

6.4. Concluding Remarks

In this chapter, preliminary investigations into an appropriate suspending agent/s for reconstitution having the ability to form an extemporaneous supporting network with tepid water were conducted. Owing to their relative ease of dispersibility and reported component synergism, a SSG-κC composite system was selected for further characterisation.

Textural and viscosity analyses were carried out on various SSG-κC systems for mechanical characterisation of the functional synergism between carrageenan and the modified starch. The presence of κC demonstrated the ability to significantly increase the compressibility in sol systems and gel systems, particularly in composite systems, demonstrative of the molecular interaction between the starch and hydrocolloid polymer components. The final viscosity of the gel systems was also significantly increased. Exploitation of κC through its functionality as a suspending and gelling agent resulted in an improvement in the textural and gel-forming properties of soluble starches such as SSG through establishment of a three-dimensional gel network.

Because of the availability of Na^+ in SSG, an additional advantage was conferred through the promotion of helix formation and/ or aggregating cross-links and gelation in the κC phase, thus allowing for weak gelation of the systems even in the absence of a quenching phase. As the concentration of κC in the system increased, its three-dimensional network spanned a greater hydrodynamic volume until the gel point was reached (in this investigation, at κC concentrations $\geq 1.0\%^{w}/_{v}$), at which point the viscosity increased dramatically and there was at least one molecule with an infinite molecular weight.

The demonstrated SSG-κC synergism, realised in terms of composite gel-forming capabilities, can thus be applied to the preparation of a pharmaceutical suspension where, in the presence of the available monovalent cations, the combination would rapidly form an aggregated supporting network with improved suspending capabilities. Further investigations focused on the identification of the optimum combination of SSG and κC for inclusion in the extemporaneous pharmaceutical suspension.