ALGINATES AS THERAPEUTIC AND

DRUG DELIVERY SYSTEMS

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SUMMARY

'Alginates as Therapeutic and Drug Delivery Systems'

Alginate is widely used as a viscosity enhancer in many different
pharmaceutical formulations. The aim of this thesis is to
quantitatively describe the functions of this polyelectrolyte in
pharmaceutical systems. To do this the techniques used were
Viscometry, Light Scattering, Continuous and Oscillatory Shear
Rheometry, Numerical Analysis and Diffusion.

Molecular characterization of the Alginate was carried out using
Viscometry and Light Scattering to determine the molecular weight,
the radius of gyration, the second virial coefficient and the Kuhn
statistical segment length. The results showed good agreement with
similar parameters obtained in previous studies.

By blending Alginate with other polyelectrolytes, Xanthan Gum and
'Carbopol', in various proportions and with various methods of low
and high shear preparation, a very wide range of dynamic rheological
properties was found. Using oscillatory testing, the parameters
often varied over several decades of magnitude. It was shown that
the determination of the viscous and elastic components is
particularly useful in describing the rheological 'profiles' of
suspending agent blends and provides a step towards the non-empirical
formulation of pharmaceutical disperse systems.

Using numerical analysis of equations describing planar diffusion,
it was shown that the analysis of drug release profiles alone does
not provide unambiguous information about the mechanism of rate
control. These principles were applied to the diffusion of
Ibuprofen in Calcium Alginate gels. For diffusion in such non-
Newtonian systems, emphasis was placed on the use of the elastic as
well as the viscous component of viscoelasticity. It was found
that the diffusion coefficients were relatively unaffected by
increases in polymer concentration up to 5 per cent, yet the
elasticities measured by oscillatory shear rheometry were increased.
This was interpreted in the light of several theories of diffusion
in gels.

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Keywords: Alginate, Diffusion, Rheogoniometer, Suspending Agents,
           Viscoelasticity.

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1. INTRODUCTION

1.1 Background

Alginate systems are capable of displaying a very wide range of physicochemical properties. The polyuronate copolymer molecules of Alginate are used mainly because of their ability to form viscous solutions, to bind divalent metal ions and to form gels. These characteristics have found wide application in many commercial areas, particularly in the food industry, eg. for enhancing viscosity, stabilising emulsions and gelling (1). The range of uses in pharmaceuticals and cosmetics is second only to the uses in foods. Alginates have been used as binders in compressed tablets (2), thickeners for suspensions (3) and in fibre form as haemostatic and absorbable dressings (4).

Alginate is a polyuronate derived from brown algae seaweed of the genus Phaeophyceae; Alginate is the principal carbohydrate component. Agar and Carrageenan possess similar gelling characteristics but are extracted from red seaweed. The acid form of Alginate, ie, Alginic acid is a block copolymer of mannuronic and guluronic acids, M and G respectively. Many of the physicochemical properties change with the relative proportion of M and G residues present in Alginate extracted from different species of Phaeophyceae (5). In the coastal waters around the British Isles, the most common species are Laminaria and Ascophyllum.

In the 1880's, Stanford first isolated and investigated

Alginic acid and its salts with several metals (6). He

thought that Alginate contained nitrogen but this was probably

due to the presence of amino acids following inadequate

purification. This was confirmed by Hoagland and Lieb in

1915 (7) who proposed H_2 $(C_{21}H_{25}O_{20})$ as the formula for

Alginic acid. After the discovery in 1926 that uronic acid,

$C_6H_{10}O_7$, was present (8, 9), investigations soon

demonstrated the present of D-mannuronic acid (10, 11).

Hirst <u>et al</u> in 1939 (12) first showed the molecule to be built

up of 1,4 - glycosidic linkages but it was not until the

chromatographic studies of Fischer and Dörfel in 1955 (13)

that the presence of L-guluronic acid was established. Hirst

and coworkers (14) then proved that M and G units were present

in the same molecule.

Following this, comprehensive studies by Haug and others (5)

at the Norwegian Institute of Seaweed Research examined the

block copolymer nature of Alginate mainly from a chemical

view-point. This work firmly established Alginate as being

composed of 1,4 - linked α ,L-guluronate and β,D-mannuronate

as shown in Figure 1.1..

Figure 1.1. The Structures of α,L—Guluronate and β,D—Mannuronate.
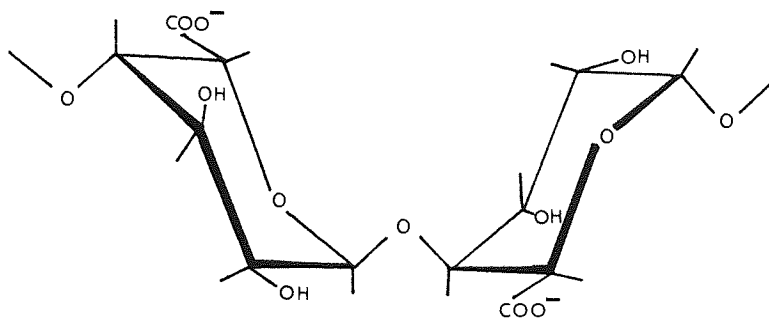
α,L-Guluronate
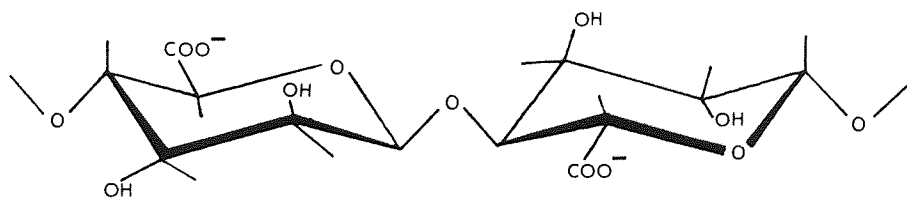
β,D-Mannuronate

1.2 Ion-Binding Properties of Alginate

The detailed chemical data for Alginate provided by Haug paved the way for other studies to apply the information to ion-binding, gelling and molecular conformation. Much of this work was carried out by Smidsrød at the same Institute (15).

All monovalent metal ion salts of Alginate are soluble except Silver, and Sodium Alginate is the most common form. All divalent metal ions except Magnesium form either insoluble salts or gels and of these, Calcium Alginate is the most commonly used. Many of the commercial applications of Alginate depend on its ability to bind Ca^{2+} ions to form gels and work in this field is of considerable interest (16, 17). One important finding of ion-exchange experiments is that the affinity of Alginates for divalent metal ions increases with increasing content of α , L-guluronate residues (18, 19). Smidsrød (15) defined a selectivity coefficient $K_A^B = X_A^B \cdot C_B^A$ where X_A^B represents the ratio of the bound fraction of incoming ion B to the bound fraction of outgoing ion A, and C_B^A represents the ratio of the concentrations of the ions A and B. Thus a high K_A^B indicates a high affinity of Alginate for ion B. He studied the exchange of Ca^{2+} for Mg^{2+} ions which resulted in a reduction of Alginate in the soluble fraction. It was found that K_{Mg}^{Ca} increased with the fraction of bound Ca^{2+} ions and Smidsrød suggested an auto-cooperative inter-chain binding mechanism whereby an initial $G - Ca^{2+} - G$ linkage

promotes the formation of further linkages by steric

advantage. The strength of the inter-chain binding is

proportional to the rigidity of the resulting gel; this

was shown by binding studies using various divalent metal

ions and comparing values of K_A^B with the mechanical strength,

(15, 20).

The specificity of Ca^{2+} ions for α , L-guluronate residues

was studied by Atkins et al (21) who used experimental X-ray

fibre diffraction and theoretical conformational calculations

to show that polyguluronate residues required water between

the chains for stability. The space so formed meant that it

was energetically favourable for guluronate residues to be

cross-linked by Ca^{2+} .   This finding led to the well known

"Egg-box" model of inter-chain binding as visualized by Rees

(22). which is illustrated in Figure 1.2..
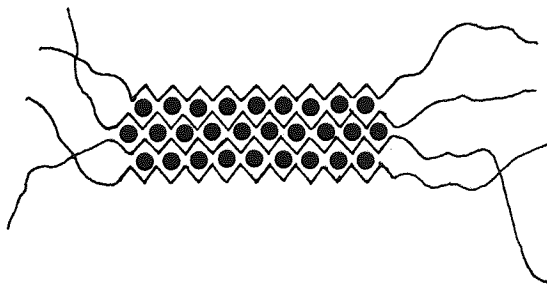
Figure 1.2.   The "Egg-box" model for inter-chain binding of Ca^{2+} ions, ● , by polyguluronate, ⋀⋀⋀ .

A recent review of polyuronate conformation and ion-binding

by Kohn (23) showed that the "Egg-box" model provides a

useful representation of inter-chain binding. These binding

sites are probably heterogeneous since the chains are unable

to pack into perfectly alligned dimers (20), but regular

packing as suggested by the "Egg-box" model, is thought to

be the main reason for high chain inflexibility, (24).

Intra-chain binding, although probably less significant in

terms of gel rigidity, is more closely defined. It has been

shown (25, 26) that single chain segments utilize a binding

site composed of COO^-, O(5), O(4) in one guluronate residue

and O(2), O(3) of the preceding unit.

1.3   Therapeutic Aspects

In addition to their role in pharmaceutical formulation, the

properties of Alginate can be of therapeutic advantage in

certain circumstances. The use of Alginate in haemostatic and

absorbable dressings has already been acknowledged. A

particular example of the application of Alginate to

therapeutic systems is a formulation of Sodium Alginate or

Alginic acid in combination with Calcium Carbonate and Sodium

Bicarbonate antacids, which is indicated for the treatment of

reflux oesophagitis (27).

The rationale is based on the precipitation of Alginic acid

from a Sodium Alginate solution in the low gastric pH.

Alginic acid is capable of absorbing several hundred times its

own weight of water (28) and thereby a swollen gel-like

precipitate is formed. The presence of Ca^{2+} ions may lead to

strengthening of the gel by the formation of Calcium Alginate

but this has not been demonstrated conclusively. On

precipitation, it is claimed that the Alginate layer forms a physical barrier to reflux (29) and in the event of reflux, the mucosa of the oesophagus is protected by a viscous layer.

Many published studies have shown that marketed formulations of Alginate with antacids are significantly more effective against reflux oesophagitis than than either Alginate alone or a placebo (30-35). The formulations contain levels of antacids below the therapeutic dosage and there is little effect on bulk gastric pH. This was demonstrated by pH measurements and was attributed to the viscous nature of the Alginate precipitate (36). The same authors also used an X-ray contrast medium to show that the gel-like precipitate covered the stomach contents for the duration of gastric residence. These findings have been supported by the work of other authors (33, 37).

Any optimization of such a therapeutic system requires the collation of clinical data and a knowledge of the ion-binding and rheological properties of, and mass transfer in, Alginate systems.

1.4   Rheology and Diffusion

In any pharmaceutical formulation containing Alginate, the mechanical characteristics of the gel or viscous solution are of prime importance. In this respect, the rheological and diffusional properties are of particular interest. The two properties are related in the simplest way by the expression

known as the Stokes-Einstein Equation (38):

$$D = \frac{RT}{6 \pi \eta N_{AV} r} \qquad \qquad 1.1$$

where D = diffusion coefficient.

      R = universal gas constant.

      T = absolute temperature.

      η = viscosity of medium

    N_{AV} = Avogadro's number.

      r = radius of spherical diffusant.

The derivation and assumptions of Equation 1.1. will be
discussed fully in Section 5.2.1.. Clearly, the Stokes-
Einstein Equation proposes that the diffusion coefficient is
inversely proportional to the viscosity of the medium in
which the solute diffuses. However, even for the free
diffusion coefficients of solutes in pure solvents,
significant deviations from Equation 1.1. have been shown to
occur according to the work of Wilke and Chang (39). These
authors used a large quantity of experimental data to collate
diffusion and viscosity, thereby obtaining an empirical
relationship.

The situation can become further complicated by the presence
of Alginate and other polymers which are viscoelastic in
solution. Here, it appears that there are two problems
involved in the correlation of diffusion and viscosity.
Firstly, we should change the rheological approach from a

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straightforward measurement of apparent viscosity to a method
that will quantify both the viscous and the elastic
components which comprise viscoelasticity. Secondly, we may
need to reappraise the relationship with diffusional
properties to take account of the elastic as well as the
viscous component of rheological behaviour.

In this thesis, emphasis is placed on the wide range of
rheological properties available by using one particular low
molecular weight Alginate in combination with other polymeric
agents. Clearly, since polyelectrolytes are widely used
adjuncts in pharmaceutical formulation, the principle is not
restricted to Alginate systems.

By combining various polymers in solution, formulations can
be 'tailored' to obtain a certain rheological profile, ie,
a viscoelastic balance of viscous and elastic properties. For
disperse systems, only recently have relationships been
proposed which correlate the settling rate of solid in liquid
suspensions with the zero shear viscosity (40) and the modulus
of elasticity (41). It is likely that such relationships,
which are based on fundamental rheological data (in contrast
to semi-empirical measurements of earlier work) will gain
widespread use in the search for a non-empirical approach to
formulation.

2.

MOLECULAR AND RHEOLOGICAL CHARACTERISTICS
OF ALGINATE SOLUTIONS

2.1. Introduction

Alginates, in common with other hydrophilic polymers such as methylcellulose, polyvinylpyrrolidone and pectin (2) are frequently used in pharmaceutical formulations as thickeners for stabilizing drug suspensions. This study is concerned with the comparison of molecular and rheological properties of Sodium Alginate in order to characterize the polymeric system.

Long polymer chains possess elastic properties when deformed. In solution, this is manifested as viscoelasticity (42) as will be explained in Section 2.2.3.. The flow behaviour of polyelectrolyte solutions is mainly a function of the coiling, or tertiary structure, of the molecule. In the case of Alginate, the chemical composition is highly variable, therefore primary and secondary structures are also important (5). Ionic strength affects the flow behaviour of Alginate (49); salt in solution causes extension of the polyelectrolyte molecule which gives rise to an increase in viscosity (50,51).

As detailed in Section 1, Alginate is a block copolymer comprised of mannuronic, M, and guluronic, G, acids; the relative proportion, or M/G ratio, depends primarily on the species of brown algae used in the extraction (47,48). In addition, the geographical region and season of harvesting can affect the M/G ratio, (46).

Because of the above properties many experimental
investigations have been carried out on Alginates in dilute
solutions. Smidsrød and Haug performed a considerable amount
of work in this field (5,15,20,52), particularly using
viscometry. Since viscometry is only an indirect method of
molecular weight determination, Smidsrød and co-workers
validated many of their results with light scattering data
(49,53,54). They showed that Alginate is a highly extended
linear flexible coil whereby the guluronic acid imparts the
greater contribution to chain rigidity. Several other studies
(16,55,56) supplement the work of Smidsrød et al, and the
contrast in results is interesting. Table 2.1. gives the
collated results from these studies, showing that as the
molecular weight of the Alginate increases, the derived
parameters do not always follow the expected trend.
All determinations were made in 0.1 M NaCl solution.

Table 2.1   <u>Molecular Properties of Sodium Alginate</u>

Weight-average Molecular weight[a] (g mol^{-1})	M/G ratio[b]	$\left(\overline{R_G}^2\right)^{\frac{1}{2}}$ [c] (nm)	$[\eta]$ [d] (dl g^{-1})	Reference
178,000	0.82	–	10.0	55
180,000	1.60	100	8.3	54
180,000	1.60	65	–	49
180,000	9.00	73	–	49
190,000	–	40	9.4	16
257,000	2.72	–	8.8	55
407,500	1.68	–	11.0	55
500,000	0.43	133	–	49
500,000	1.60	105	–	49
525,000	1.60	122	10.1	53
690,000	5.67	200	17.0	56
880,000	0.33	260	25.0	56
1,670,000	19.0	370	28.5	56

a.   Determined from light scattering measurements
b.   Ratio of the mannuronic to guluronic acid content in alginate.
c.   Root-mean-square radius of gyration from light scattering measurements.
d.   Intrinsic viscosity.

Light scattering and viscometry are both methods for which extrapolation to zero concentration is necessary and therefore, very dilute solutions are used to minimize polymer - polymer interactions.

At the other extreme of the concentraction range, polymer entanglement is observed (57). The concentration at which entanglement is seen, is entirely dependent on the molecular weight and other such properties of the polymer. Certain details of molecular conformation in entanglements can then be obtained from rheological measurements, (58,59).

However, in the concentration range intermediate between dilute and entangled polymer solutions, viscoelastic phenomena are observed for which interpretation in terms of molecular conformation is possible only for the simplest models (45,60).

In this study, a low molecular weight Alginate was used to contrast the molecular characteristics obtained by viscometry and light scattering, with the rheological properties obtained from continuous shear and oscillatory rheometry.

2.2   Theory

2.2.1 Viscometry

In contrast to the absolute methods of molecular weight determination such as the colligative methods and light scattering, viscometry is a relative method. This is because

the mechanical behaviour measured is only a reflection of the actual molecular dimensions. For this reason, viscometry results should always be calibrated against an absolute method.

Staudinger (61) first showed an empirical relationship between the molecular weight and the specific viscosity, η_{sp}, for polystyrene solutions, given in Equation 2.1.

$$\eta_{sp}/c = K_m M \qquad\qquad 2.1.$$

where $\quad \eta_{sp} = \eta r - 1 = (\eta/\eta_0) - 1$

$$\eta_r = \text{relative viscosity}$$

$$\eta = \text{solution viscosity}$$

$$\eta_0 = \text{solvent viscosity}$$

$$K_m = \text{constant}$$

$$M = \text{molecular weight}$$

$$c = \text{concentration of polymer in solvent}$$

By extrapolation to zero concentration, the intrinsic viscosity is obtained, ie $[\eta] = (\eta_{sp}/c)_{c \to 0}$, representing the capacity of a polymer to enhance the viscosity. The so-called modified Staudinger Equation is then obtained from Equation 2.1.

$$[\eta] = K_m M_\eta^{\alpha} \qquad\qquad 2.2$$

where $\quad M_\eta = \text{viscosity average molecular weight}$

$$\alpha = \text{exponent}$$

It should be noted that $M_\eta = M_w$, the weight-average molecular weight, only when the exponent, $\alpha = 1.0$ (62). Although this

equation was developed empirically, theoretical justification
was later shown for random coil structure by Kuhn (65),
Huggins (66) and Kramer (67), notably for theta conditions
where the exponent $\alpha = 0.5$ (68). This gives Equation 2.3.

$$[\eta]_\theta = K_\theta M_\eta^{0.5} \qquad\qquad 2.3.$$

In practice, theta, θ, conditions are achieved at a particular
critical temperature and in a particular solvent system such
that there are negligible polymer-solvent interactions. Hence,
the polymer exists in an unperturbed state. If theta
conditions have not been determined, as is the case for
Alginate, the best approximation is achieved by measuring $[\eta]$
at increasing ionic strength, μ, and then extrapolating to $\mu = \infty$

The unperturbed dimensions have been frequently determined in
this manner (52,69,70). It is thought that the polyelectrolyte
is in an effectively uncharged state at $\mu = \infty$ because the
salt swamps the fixed charges on the polymer so that the mutual
repulsion between polymer and solvent is effectively removed.
Smidsrød found that for Alginate, $[\eta]$ at $\mu = \infty$ was quite high
and corresponded to an exponent α value of 0.84, (20,71).

The deviation of the exponent α from 0.5 gives a measure of
the extension of the polymer. As a guide, if $\alpha = 0.5 - 0.8$,
the molecules are randomly coiled; $0.8 - 1.8$ indicates a
stiffly coiled molecule and 1.8 a rigid rod, (72).

Flory and Fox pointed out that $[\eta]$ should be proportional to
the ratio of the volume occupied by the molecule and the

molecular weight, (75,76). This is emcompassed in Equation 2.4. (32):

$$[\eta] = \frac{\Phi(\overline{r}^2)^{3/2}}{M_\eta} \qquad 2.4.$$

where Φ = Flory constant

Φ = 0.01588 $(\pi/6)^{3/2}$. N_{av} = 3.62 x 10^{21}

N_{av} = Avogadro's number

$(\overline{r}^2)^{1/2}$ = Root-mean-square end-to-end distance of chain (cm).

It was originally claimed that Φ is independent of the characteristics of the molecule provided it is a random coil. However, other values of Φ = 2.0 x 10^{21} (77) and Φ = 2.86 x 10^{21} (78) have been determined. Bloomfield and Zimm (79) introduced the expansion factor ε to express the deviation of a polymer chain from the dimensions defined by a Gaussian distribution. They considered deviations due to excluded volume (free draining) effects, polyelectrolyte (non-draining) effects, or mechanical chain stiffness. From a knowledge of ε, values of the Flory constant $\Phi(\varepsilon)$ can be calculated using Equation 2.5.

$$\Phi(\varepsilon) = 2^{-\varepsilon/2} N_{av} (2\pi^3)^{1/2} (6 + 5\varepsilon + \varepsilon^2) \frac{1}{24} \left(\sum \lambda'_k{}^{-1} \right) \qquad 2.5.$$

where $\varepsilon = \frac{(2\alpha - 1)}{3}$ from Elias (67)

$\sum \lambda'_k{}^{-1}$ = summed reciprocal eigenvalues

Values of $\Phi(\varepsilon)$ were tabulated by Bloomfield and Zimm (79) and range from 2.81 x 10^{21} for ε = 0 to 0.686 x 10^{21} for ε = 0.5, in straight chain polymers.

2.2.2 Light Scattering

The use of light scattering as a technique for studying the molecular properties of polymer solutions is well established (73,80,81). In 1871, Lord Rayleigh (82) first showed that the intensity of light scattered by small particles in gases is inversely proportional to the fourth power of the wavelength of incident light. The theoretical application of this principle to molecules in solution is due to Mie in 1908 (83) and Einstein in 1910 (84); the practical development of this theory was carried out by Debye from 1944 (85,86). It was found that the intensity of light scattered by a polymer solution is related to its molecular mass, M_w, by Equation 2.7.

$$\frac{Kc}{R_\theta} = \frac{1}{M_w} + 2Bc + 3Cc^2 + \ldots \qquad 2.7.$$

where c = concentration

$$K = \frac{2\pi^2 n_0^2}{N_{av} \lambda_0^4} \left(\frac{dn}{dc}\right)^2 \qquad 2.8.$$

dn/dc = refractive index increment of polymer solution.

n_0 = refractive index of solvent.

λ_0 = wavelength of incident beam.

R_θ = Rayleigh ratio = $\dfrac{r^2 i_\theta}{I_0 (1 + \cos^2\theta)}$ $\qquad 2.9.$

i_θ = intensity of light scattered at angle θ at a distance r between sample and observation port.

I_0 = intensity of incident radiation

B = Second virial coefficient

C = Third virial coeffecient

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The expression is greatly simplified on extrapolation to zero concentration and angle.

$$\left[\frac{Kc}{R_\theta}\right]_{\substack{\theta \to 0 \\ c \to 0}} = \frac{1}{M_w} \qquad \text{2.10.}$$

In the case of the 'SOFICA' light scattering instrument used in this study, benzene was employed as a standard for converting the instrument meter reading to absolute scattering intensity by Equation 2.11. (87):

$$R_\theta = R_b \left(\frac{\alpha I_\theta}{I_b}\right) \left(\frac{n}{n_b}\right)^2 \qquad \text{2.11.}$$

$$\text{where} \quad \alpha = \frac{\sin \theta}{1 + \cos^2 \theta} \qquad \text{2.12.}$$

R_b = Rayleigh ratio of benzene at 25^0 C
  = 16.3×10^{-6} .

I_b = Galvanometer deflection for benzene

I_θ = Galvanometer deflection for solution in excess of the solvent contribution = $i_\theta - I_0$.

n = refractive index of solution

n_b = refractive index of benzene.

$\sin \theta$ = correction factor for converting scattering volume viewed at angle θ into that at 90^0 .

$1 + \cos^2 \theta$ = correction for use of unpolarised light.

By substituting R_θ in Equation 2.11. into Equation 2.10 we obtain

$$\frac{2\pi^2 n_b^2}{N_{av} \lambda_0^4 R_b} \left(\frac{dn}{dc}\right)^2 (I_b) \left[\frac{c}{\alpha I_\theta}\right]_{\substack{\theta \to 0 \\ c \to 0}} = \frac{1}{M_w} \qquad \text{2.13}$$

The terms N_{av}, R_b, n_b and λ_0 are all independent of the polymer-

solvent system and can be substituted to obtain

$$0.506 \left(\frac{dn}{dc}\right)^2 (I_b) \left[\frac{c}{\alpha I_\theta}\right]_{\substack{\theta \to 0 \\ c \to 0}} = \frac{1}{M_w} \qquad 2.14.$$

where n_b = 1.496
λ_0 = 54.61 x 10^{-6} cm
N_{av} = 6.023 x 10^{23}

By plotting the experimental data as a Zimm plot of $c/\alpha I_\theta$

against $\sin^2 \theta/2$ + kc where k is an arbitrary constant, then

extrapolations to zero concentration and zero angle are

possible. Hence, M_w is obtained from Equation 2.14. Other

parameters which can be determined are the root-mean-square

radius of gyration $(R_G^2)^{\frac{1}{2}}$ from Equation 2.15. and second

virial coefficient, B, from Equation 2.16.

$$(R_G^2)^{\frac{1}{2}} = \frac{3\lambda}{2\pi\sqrt{2}} \left[\frac{\text{Slope of line c = o}}{\text{intercept}}\right]^{\frac{1}{2}} \qquad 2.15.$$

where $\lambda = \frac{\lambda_0}{n_0}$

$(R_G^2)^{\frac{1}{2}}$ is defined as the root-mean-square distance of any

element of a molecule from the centre of gravity of that

molecule.

$$B = 0.506 \left(\frac{dn}{dc}\right)^2 (I_b) \frac{(\text{Slope of line } \theta = o)}{2} \qquad 2.16.$$

The second virial coefficient is frequently neglected in

molecular studies because it relates not to molecular

dimensions, but to the thermodynamics of the solvent with

respect to the polymer it contains (86). In an ideal solution,

there is no change in the properties of polymer or solvent on

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mixing and B is negligible. Therefore B provides a measure
of the closeness to ideality and of the accuracy of the
extrapolation used to obtain Equation 2.10. from Equation 2.7..
B decreases with M_W (87) and with ionic strength (74).

Another molecular parameter frequently used by Smidsrød
(15,20,52,53) is the Kuhn statistical segment, A_m, introduced
by Kuhn in 1951 (88) to model a molecule in terms of N_m
straight chain segments, each of length A_m.

If the mean-square end-to-end distance of the molecule is $\overline{r}^2$,
then A_m is given by Equation 2.17.

$$A_m = \frac{\overline{r}^2}{b_0 P} \qquad\qquad 2.17.$$

    where P = degree of polymerisation

    and b_0 = monomer length

b_0 = 5.15 x 10^{-8} cm for each uronic acid residue (89).
$\overline{r}^2$ can be related to the radius of gyration obtained from
light scattering experiments by:

$$R_G^2 = \frac{\overline{r}^2}{6} \qquad\qquad 2.18.$$

It is now clear that a considerable amount of information
about the molecular characteristics of Alginate can be
obtained from viscometric and light scattering studies.

2.2.3 Rheology

In rheological studies of materials, there are three basic
experimental methods available, namely continuous shear, creep

compliance and oscillatory testing (43,90). The principles, derived parameters and illustrations of the data obtained for each method are summarised in Table 2.2. and Figure 2.1.. The continuous shear technique is distinguished from the other two methods by its inability to fully characterise materials of a viscoelastic nature. Firstly, it is necessary to understand the term viscoelasticity.

Hooke's law of elasticity and Newton's law of viscosity explain the two extremes of flow behaviour. However, there are numerous materials, many of pharmaceutical interest such as ointments, gels and suspensions, (91), whose flow behaviour follows neither classical hypothesis, except perhaps at infinitessimal rates of strain for predominently viscous materials or at infinitessimal strains for predominantly elastic materials. Such materials are termed viscoelastic since they possess both viscous and elastic properties. If the material does not continually deform when stress is applied, then it is a viscoelastic solid; otherwise it is known as a viscoelastic liquid.

The shortcomings of the continuous shear testing method therefore arise from the inability to measure elastic components. For pharmaceutical materials especially, these inadequacies have been listed elsewhere by Barry (91) and Davis (92,93). The readings obtained from a continuous shear 'rheogram' do not provide fundamental rheological parameters; they measure the stresses that occur as the structure is

Table 2.2. Principles and Parameters of Rheological Testing

Method	Input Function	Output Function	Protocol	Parameters obtained	Traditional Units	Equivalent S.I. Units
Continuous Shear	Rate of Strain	Stress	Sample is sheared between two surfaces	Apparent Viscosity	Poise	10^{-1} Pa s
				Apparent Yield Values	Dyne cm^{-2}	10^{-1} Nm^{-2}
				i. dynamic $\tau(d)$ ii. static $\tau(s)$		
				Area of hysteresis loop.	Dyne cm^{-2} s^{-1}	10^{-1} Pa s^{-1}
Creep Compliance	Stress	Strain	Stress is applied to one of the surfaces in contact with the sample.	Compliance $J(t)$ (reciprocal elasticity)	Cm^2 dyne^{-1}	10^{1} m^2 N^{-1}
				Retardation times	S	S
Oscillatory Testing	Strain	Stress	Sinusoidally oscillating Signal of low amplitude is applied to one surface	Real and Imaginary Moduli G' and G"	Dyne Cm^{-2}	10^{-1} Nm^{-2}
				Real and Imaginary Viscosities η and η	Poise	10^{-1} Pa s

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Figure 2.1   The Form of Experimental Data from Rheological Testing

a.   Continuous
     Shear

b.   Creep
     Compliance

J_0 = initial shear compliance

$J(t)$ = time-dependent compliance
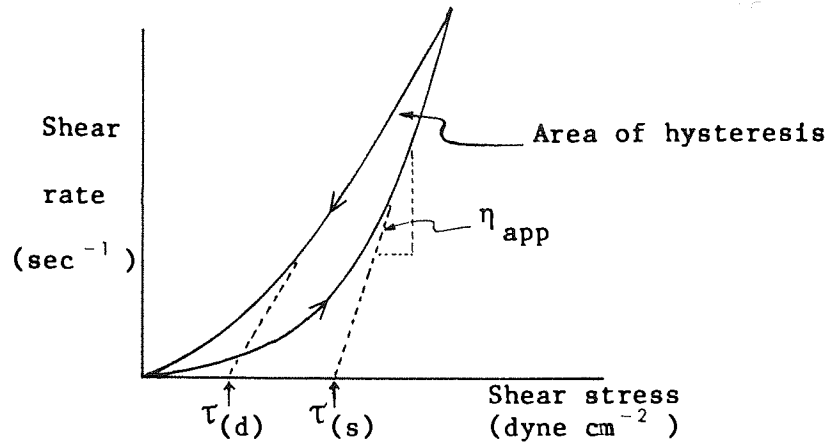
J_N = Newtonian compliance
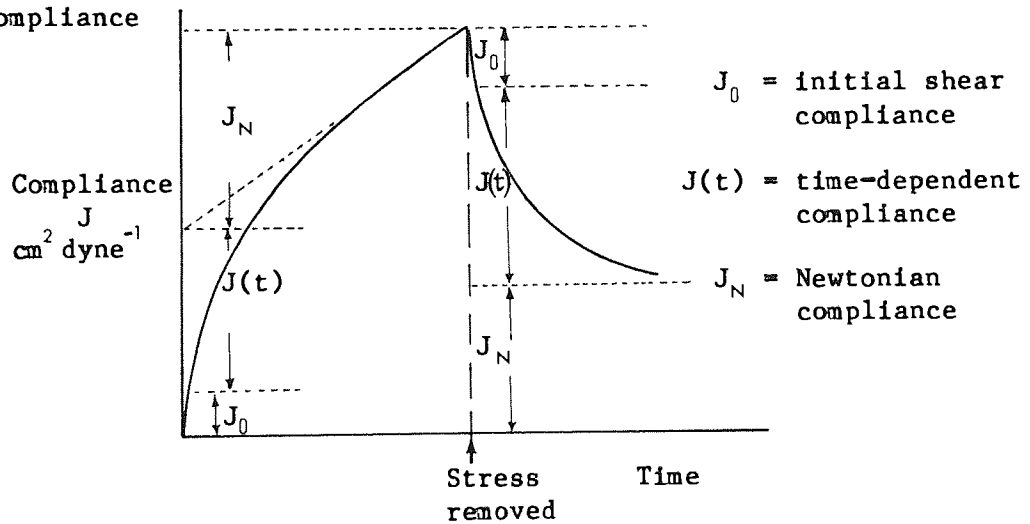
c.   Oscillatory
     testing
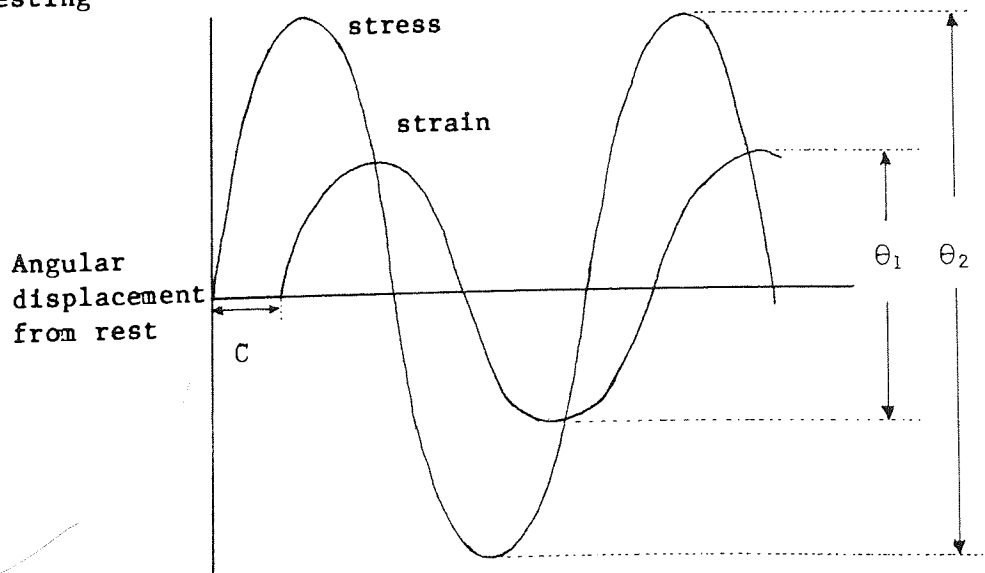
C = Phase difference between stress and strain waves.

ν = Amplitude ratio = θ_1 / θ_2

broken down. The parameters derived are often only of use in comparative studies. Many theories have been proposed in attempts to overcome this problem, by fitting of the non-Newtonian flow-curve to various equations and often ascribing physical significance to certain coefficients. Notable examples are summarised in Table 2.3.. Cheng (100) has suggested that such semi-empirical equations should be used freely to allow the best possible expression of continuous shear data for comparative purposes.

Table 2.3   Quantitative Descriptions of Non-Newtonian Behaviour

Equation	Parameters	Reference
$\tau = k\dot{\gamma}^N$	k and N are empirical constants	Metzner (94)
$\tau = \tau_y + \eta_p \dot{\gamma}$	Yield value = τ_y Plastic viscosity = η_p	Bingham (95)
$\tau^{\frac{1}{2}} = \tau_y^{\frac{1}{2}} + k\dot{\gamma}^{\frac{1}{2}}$	Yield value = τ_y Empirical constant = a	Casson (96)
$\tau = f + \eta_\infty \dot{\gamma} - b_v e^{-a\dot{\gamma}}$	Yield value = $f - b_v$ Infinite shear viscosity = η_∞ Empirical constant = a	Shangraw et al (97)
$\tau = \eta_\infty \dot{\gamma} + f(1-e^{-a\dot{\gamma}})$	As above but yield value = 0	Yakatan et al (98)
$\eta_{app} = \eta_\infty + \left(\dfrac{\eta_0 - \eta_\infty}{1 + \alpha\dot{\gamma}^{2/3}} \right)$	Zero Shear viscosity = η_0 Empirical constant = α	Cross (99)

Creep compliance testing has not been used in this study of

Alginate solutions and gels and will not be discussed in

detail. Suffice it to say that J(t) can be analysed in terms

of Maxwell and Voigt mechanical models thereby giving various

retardation times. A retardation time gives a measure of the

relaxation of strain on removal of stress. The technique has

been widely applied to pharmaceuticals in general (91,101-103)

and has also been used for Alginate gel systems by Mitchell and

Blanchard, (104,105).

In oscillatory testing, the experimental data is obtained in

terms of the amplitude ratio, ν and the phase difference, C as

shown in Figure 2.1.c. The instrument used in this study was

the Weissenberg Rheogoniometer described in Section 2.3.4.2..

The theory for forced oscillatory testing developed by Walters

and Kemp (106) is most readily illustrated for the parallel

plate geometry (107,108). During testing, when the sample

behaves as a perfectly elastic solid, then the phase difference

between the two surfaces is zero and the energy is stored; a

perfectly viscous liquid would give a phase difference of $\pi/2$

rad between input and output, and the energy involved is

dissipated as heat. Because of the difficulty in expressing

viscous and elastic components in one term, convention dictates

that complex variables be used. Hence, we obtain the complex

modulus of elasticity G* and the complex viscosity η*, (43,90),

given by Equations 2.19 and 2.20 respectively.

$$G* = G' + iG''$$ 2.19

$$\eta* = \eta' - i\eta''$$ 2.20

where G' = storage modulus

G" = imaginary or loss modulus = $\eta'\omega$

η' = dynamic viscosity

η'' = imaginary viscosity = G'/ω

ω = radian frequency = $2\pi n_f$

n_f = frequency of oscillation in Hz.

The theory for parallel plate geometry (106) gives the result:

$$\frac{\exp^{iC}}{\nu} = \cos\alpha h + S\alpha h \sin\alpha h \qquad 2.21.$$

where $S = \dfrac{2}{\pi\rho a^4 h}\left(\dfrac{K}{4\pi^2 n_f^2} - I\right) \qquad 2.22.$

I = moment of inertia of instrument members

$$= \frac{K_t}{4\pi^2 n_a^2}$$

ρ = density of sample

a = radius of platen

h = gap between parallel plates

K_t = torsion bar constant for the instrumental in dyne cm μm^{-1}

n_a = free oscillation frequency of torsion bar, ie, in air.

$$\alpha = -\frac{i\omega\rho}{\eta^*} \qquad\qquad 2.23.$$

α = "fundamental inertia parameter"

$i = \sqrt{-1}$

Expression of Equation 2.21 in terms of α and substitution of η' for η^* in Equation 2.23 should allow the derivation of η' from experimental ν and C values. In practice this is

a difficult mathematical manoeuvre (106) but fortunately, approximate equations for η' and G' are available provided that $\alpha h \ll 1$(107).

$$\eta' = \frac{-2\pi n_f \rho S h^2 \nu \operatorname{Sin} C}{(-2 \operatorname{Cos} C + 1)} \qquad 2.24.$$

$$G' = \frac{4\pi^2 n_f^2 \rho S h^2 \nu (\operatorname{Cos} C - \nu)}{(\nu^2 - 2\nu \operatorname{Cos} C + 1)} \qquad 2.25.$$

α is a fundamental parameter which is dependent on the inertia present in a sample during a test. High frequencies used for thin fluids result in high values of α; low α values occur at lower frequencies (thick fluids). Walters and Kemp (106) showed that for a Newtonian liquid of viscosity 0.1 poise, the neglect of fluid inertia in the αh term leads to significant errors only at frequencies above n_a, the natural frequency of the rheogoniometer torsion bar. It therefore seems reasonable that measurement of samples showing viscosities greater than 0.1 poise at frequencies below n_a should not lead to significant errors caused by neglect of fluid inertia.

Oscillatory testing leads to the expression of η' and G' as functions of the frequencies ω, ie, $\eta(\omega)$ and $G'(\omega)$. These are the relationships which describe the viscoelasticity.

In conclusion it should be noted that the three methods of rheological testing may be inter-related. Values of $J(t)$ can be determined from a knowledge of $G'(\omega)$ and vice-versa (44).

Cox and Merz proposed an empirical rule to relate the apparent viscosities at known shear rates to the absolute values of the complex viscosity at corresponding frequencies (109). Similar theories have followed (110,111) and recently, Williams (112) has suggested a method of obtaining viscometric data from a 'Brookfield' continuous shear viscometer.

2.3 Materials and Methods

The Sodium Alginate used was Protonal LFR5/60[1] which is a low molecular weight grade produced by degradation of Alginate from Laminaria hyperborea stipes.

2.3.1 Viscometry

Viscometry measurements were carried out using a U-tube viscometer[2] immersed in a water bath at 25 ± 0.1^0 C. In order to determine η_{sp} values to an accuracy of $\pm$ 1%, alginate concentrations were chosen such that $1.2 < \eta_r < 2.0$ relative to the calibration standard of water (28). Solutions were prepared from a 1% w/v solution in 0.1 M NaCl by stirring for 16 hours followed by dialysis against 0.1 M NaCl for 4 days. The dialysis tubing was boiled in double distilled water for 30 min. and rinsed prior to use.

Values of η_r were obtained using Equation 2.26

$$\eta_r = \eta/\eta_0 = \frac{\rho t}{\rho_0 t_0}$$
2.26.

where η_r = relative viscosity

ρ = density of solution

ρ_0 = density of solvent = 0.99707 g cm^{-3} at 25^0 C. (113).

[1] Protan A/F , Norway.
[2] Ostwald viscometer, Size A
[3] Grant Instruments, Cambridge, England

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η = solution viscosity

η_0 = solvent viscosity = 0.008904 poise at 25^0 C

$$(114)$$

t = time taken by the solution

t_0 = time taken by the solvent

The y-intercept of the linear plot of $\eta sp/c$ against c gave values of $[\eta]$ in the conventional units of dl g^{-1}. Density determinations were made using a 25 ml glass specific gravity bottle calibrated with water at 25^0 C.

2.3.2 Light Scattering

Light scattering measurements were made using a Photo Gonio Diffusometer[1]. The instrument has been used previously for studying alginate (55,117) and is described in detail by Chiang (87). In principle, an unpolarised beam of monochromatic light (mercury source λ_0 = 546.1 nn) passes through the cell containing the sample; the scattered light is detected, and amplified by a photomultiplier to be displayed as a galvanometer reading, I. A constant temperature of 25^0 C was maintained using an external source of water circulation[2].

Marked dissymmetry of the Zimn plot can occur if solutions are contaminated with dust particles, therefore cleanliness and clarification are important. All glassware was soaked over-night in chromic acid cleaner, thoroughly rinsed with water and finally rinsed under laminar flow conditions with double distilled[3] and filtered (1.0 μm) water.

[1] S.O.F.I.C.A., Model 42000, Le Mesnil-Saint-Denis, France.
[2] Churchill Thermocirculator, Churchill Inst.Co.Ltd., Perivale, Middlesex, U.K.

[3] 'Fi-stream' all glass still, Fisons.

The light scattered by $2 \times 0.2 \mu m$ filtered benzene was compared to that of the glass standard provided. The manufacturer's calibration was found to be valid, ie.,

$$0.92 = \frac{R_{90^0} \text{ (glass)}}{R_{90^0} \text{ (benzene)}} = \frac{\text{Scale Reading at } 90^0 \text{ (glass)}}{\text{Scale Reading at } 90^0 \text{ (benzene)}}$$

The light scattered by the glass standard and the benzene were symmetrical in the range $30^0 - 150^0$ indicating that the benzene in the vat was free of dust.

Clarification of the Alginate solutions was carried out by three regimens of centrifugation and filtration as shown in Table 2.4.

Table 2.4   Clarification of Alginate Solutions

Centrifugation		Filtration	
g-force	Time (hr.)	Temperature (^{0}C)	
3000 [1]	2	20	$1 \times 0.45 \mu m$
25,000 [2]	2	4	$4 \times 0.45 \mu m$
100,000 [3]	2	4	$4 \times 0.45 \mu m$

The intensities of light scattered by the samples were measured in order of increasing angle and increasing concentration, with the use of a Y – T chart recorder[4]. Readings were adjusted to correspond to the sensitivity used for the benzene standard and the intensity due to the solvent alone was then subtracted to

[1] Hereaus Christ 03400, V.A.Howe & Co Ltd, Peterborough Rd, London SW6, UK.
[2] MSE High Speed 18 } MSE Scientific Instruments, Crawley, Sussex, UK.
[3] MSE Superspeed 50 }
[4] Bryans Model 28000, Bryans Limited, Mitcham, Surrey, U.K.

obtain values of I_θ, see Section 2.2.2. A Zimm plot may then

be constructed by plotting $c/\alpha I_\theta$ against $\sin^2\theta/2 + kc$.

2.3.3 Determination of Alginate Content

Alginate solutions were assayed for uronic acid content based

on the Phenol-Sulphuric Acid method of Dubois (116). The

mechanism of this reaction (145) is summarised in Scheme 2.1.

below.

Scheme 2.1. The Reaction of a Uronic Acid with Concentrated
Sulphuric Acid and Phenol.

D-Mannuronic acid
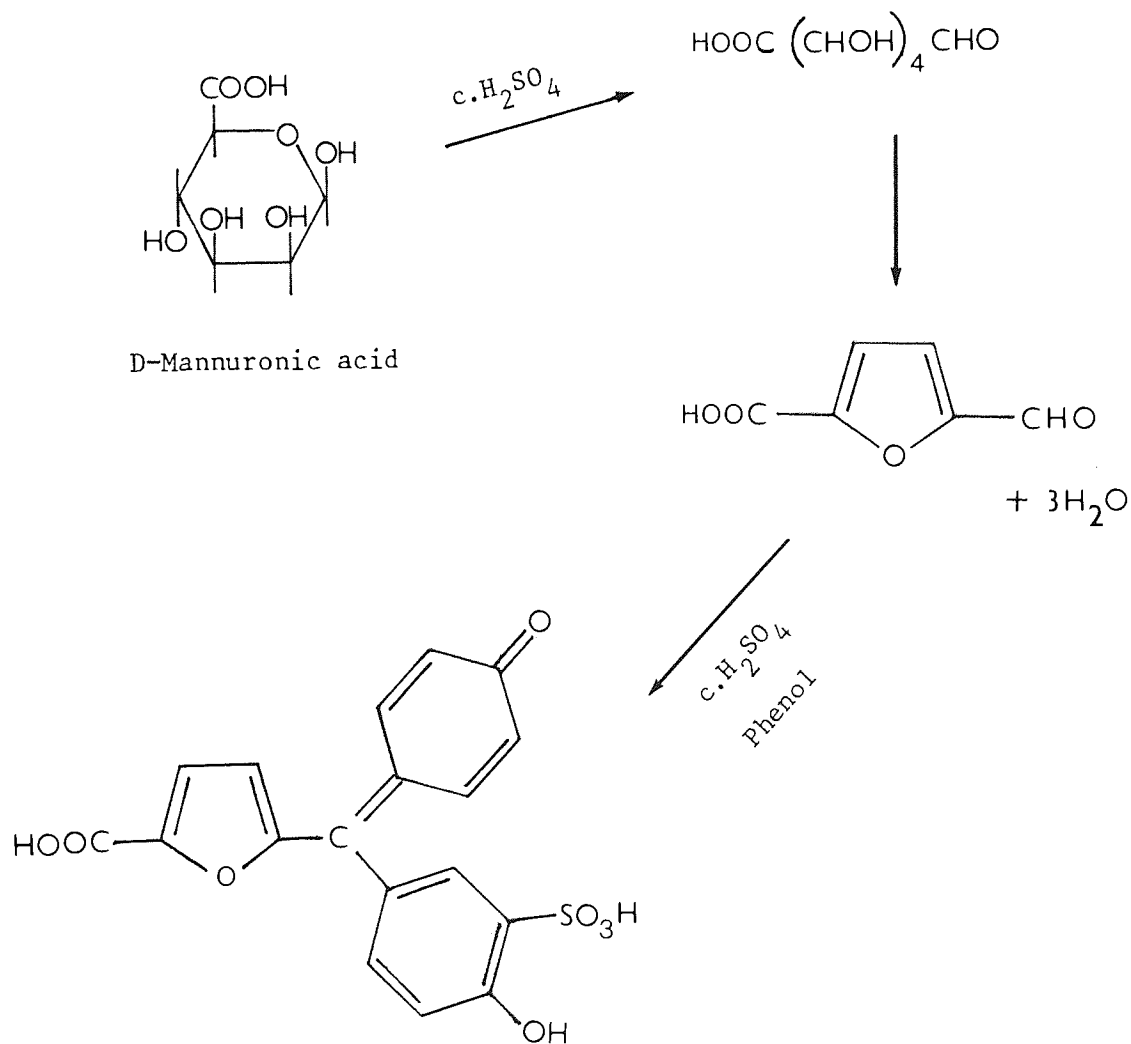
Phenol sulphonic acid furan derivative, λ_{max} = 285 nm.

Standard solutions for calibration were prepared using Alginate which had been dried to constant weight immediately prior to use. The procedure was as follows:

1. Add 0.5 cm^3 of 5% w/w Phenol solution to 2 cm^3 solution. containing 10-200 μg of Alginate.

2. Add 5 cm^3 of conc. H_2SO_4[a] rapidly.

3. Stir carefully with a glass rod.

4. Shake in a water bath at 25°C for at least 20 minutes.

5. Read the UV-absorbance at 285 nm.

2.3.4 Determination of Refractive Index Instrument.

Values of dn/dc were determined using a differential refractometer[b] calibrated with ten NaCl solutions.

A 1% w/v solution of Sodium Alginate in 0.1 M NaCl was diluted to give a range of concentrations from 0.1 to 1.0% w/v. The mean of six readings of refraction distance were taken in each case.

2.3.5 Rheology

A Weissenberg Rheogoniometer model R16[c] was used in a constant 20°C temperature laboratory, for both continuous shear and oscillatory shear experiments. Figure 2.2 shows the main

[a] AR grade; e.g. = 1.84 g cm^{-3}
[b] Phoenix Precision Instruments
[c] Sangamo Controls Ltd., Bognor Regis, Sussex. U.K.

Figure 2.2. The Weissenberg Rheogoniometer model R16

1. Three phase motor 1500 rpm output
2. 60 speed-setting gearbox
3. Variable sine wave generator
4. Worm screw
5. Lower platen
6. Sample
7. Upper platen
8. Air bearing
9. Clamp
10. Torsion bar
11. Clamp
12. Armature
13. Torsion head transducer
14. Gap setting transducer
15. Input function transducer
16. Torsion head transducer meter
17. Gap setting transducer meter
18. Input transducer meter
19. UV chart recorder

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components of this instrument; its functioning has been
described elsewhere (91). Basically, the lower member is
rotated or oscillated and the response of the sample in the
gap is measured by angular displacement of the upper member
via a torsion bar and distance transducer assembly. Different
speeds of rotation or frequencies of oscillation are achieved
by a manual change gearbox.

2.3.5.1 Continuous Shear Experiments

The continuous shear behaviour of Alginate solutions in 0.1 M
NaCl was carried out for the concentration range 0.25 - 10.0
g dl^{-1}. Cone and plate geometry was used; the diameter was
7.5 cm and the non-truncated cone angle was $1^0 32'$. The gap
between the cone and plate was set to 0.061 mm using the gap-
setting transducer. The torsion bar used was of Size No. 7
with K_t = 104 dyne cm μm^{-1}. The shear rate range used was
0.5855 to 1467 sec^{-1} and the shear stress was obtained from
transducer meter readings. The calibration was checked using
water and Silicone Fluid 100 cs. The viscosity of the latter
was determined using a calibrated U-tube Ostwald Viscometer.
Values of η obtained using the Rheogoniometer and the Ostwald
viscometer differed by no more than 4%.

2.3.5.2 Oscillatory Shear Experiments

The oscillatory shear behaviour of Alginate solutions in double
distilled water was carried out for the concentration range 5.0
to 20.0 g dl^{-1}. Parallel plate geometry was used with 7.5 cm
plates and the gap between the plates was set to 0.508 mm

throughout. The input and output waveforms were recorded on UV-chart paper[1] from which the amplitude ratio, ν, and phase lag, C, were determined graphically. Values of ν and C were substituted into Equations 2.24 and 2.25 to obtain η' and G'. The natural frequency of the torsion bar (Size No.7) was found to be 4.00 Hz and therefore the range of frequencies used for measurements was 7.91×10^{-3} to 3.97 Hz. Anomalies in readings taken near the natural frequency are known to occur, therefore it is wise to avoid these measurements, (108,117,118).

The calibration of the gap-setting, torsion head and oscillation transducers was carried out using a micrometer; the latter two transducers were also calibrated with respect to the UV chart paper and appropriate adjustments were made.

In order to check the oscillatory function of the rheogoniometer, tests were carried out using the Newtonian liquids Silicone Fluid 100 cs, and Liquid Paraffin B.P. to obtain (ν, ω) and (C, ω) curves. Theory dictates that when $\omega = \omega_0$, $\nu = 1$ and $C = 0$. In addition, a viscoelastic sample of Carbopol 941[2] 1% w/w was tested in order to compare the values of η' and G' with those obtained by Barry (119).

2.4 Results

2.4.1 Viscometry

Calibration of the Ostwald viscometer with double distilled water at 25^0C yielded t_0 = 277.50 $\pm$ 2.23 sec, which was a sufficiently long time to negate the need for kinetic energy correction (120). The density of a 1.0 g dl^{-1} solution of Sodium Alginate was found to be 1.00505 g cm^{-3}. Although small, the density correction of 0.8% was ten times greater than the standard deviation of the viscometer times and was therefore used in Equation 2.26..

The results given in Tables 2.5(a) and (b) are for Alginate solutions before and after ultracentrifugation. Each value represents the mean of three t-determinations for each of two sample solutions used in the viscometer. The linear plots of η_{sp}/c against c given in Figure 2.3 gave least mean square correlation coefficients in excess of 0.99; $[\eta]$ = 1.056 $\pm$ 0.05 dl g^{-1} before and $[\eta]$ = 1.046 $\pm$ 0.12 dl g^{-1} after ultracentrifugation.

Due to the variable nature of Alginate several values of K and exponent α for the modified Staudinger Equation 2.2 are to be found in the literature. The values of K = 2.0 x 10^{-5} and α = 1.0 (ionic strength μ = 0.1) have been determined by Smidsrød (52) for Alginate from L.digitata with M/G = 1.60. This would provide the viscosity-average molecular weight, M_η = 52,000g mol^{-1}. The K and α values of Mackie et al. (56) do not

Table 2.5 Viscometric Data

(a) Intrinsic viscosity determination before
     ultracentrifugation.

Concentration (g dl^{-1})	Mean Viscometer time (secs)	η_{sp}/c (dl g^{-1})
0.12	315.61	1.154
0.2	342.39	1.179
0.4	427.47	1.363
0.6	524.23	1.497
1.0	765.83	1.782

(b) Intrinsic viscosity determination after
     ultracentrifugation at 100,000 x g for 2 hr.

Nominal Concentration (g dl^{-1})	Assay Concentration (g dl^{-1})	Mean Viscometer time (secs)	η_{sp}/c (dl g^{-1})
0.4	0.376	414.40	1.286
0.8	0.696	579.75	1.582
1.0	0.906	700.16	1.701
1.4	1.182	880.94	1.865

Figure 2.3. Determination of the Intrinsic Viscosity, $[\eta]$, of Alginate from a plot of Reduced Viscosity against Concentration.

Before Centrifugation ● and After Centrifugation ○ .

Figure 2.3 (see facing page).

Reduced Viscosity η_{sp}/c (dl g^{-1})

Alginate Concentration c(g dl^{-1}).
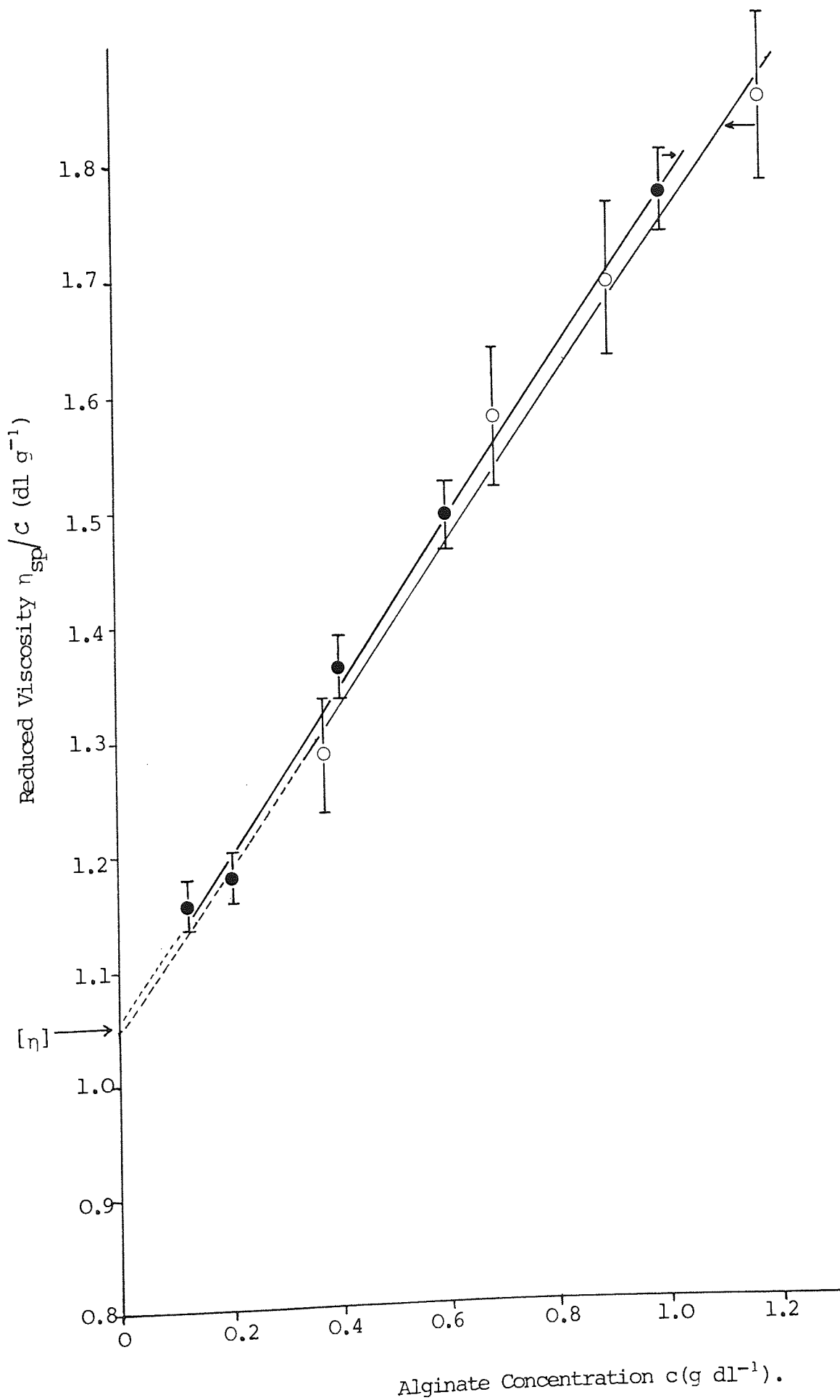
appear to follow any simple relationship with respect to the

M/G ratio and consequently, the calibration of $[\eta]$ from the

weight average molecular weight, M_w, is necessary for each

Alginate sample used. To do this, Smidsrød and Mackie

utilised fractionation by acid hydrolysis of a high molecular

weight Alginate. In contrast, Protonal LFR5/60 Sodium

Alginate is already a low molecular weight polymer as reflected

by the $[\eta]$ values, therefore calibration by hydrolysis would be

difficult. By substituting for $[\eta]$ using K and α values due to

Mackie et al, values of M_η ranging from 35,400 to 59,300 g mol^{-1}

are obtained. Clearly, the use of viscometry alone is

insufficient to characterise the Alginate.

The higher standard error limits of $[\eta]$ for the

ultracentrifuged solutions are due to errors involved in the

phenol-sulphuric acid assay. The mean calibration line

follows Equation 2.27.

$$\text{Absorbance} = (63.1 \pm 1.3) \; c + (0.046 \pm 0.014) \qquad 2.27$$

$$\text{where } c = \text{concentration in g dl}^{-1}$$

The assay method is sensitive to approximately $\pm$ 10 µg and

inevitably, some errors are introduced during the dilution of

stock solutions to achieve such low concentrations. The

assay of a 1.0 g dl^{-1} dialysed stock solution after

centrifugation at 3000 g for 2 hr. gave a response line with

a slope not significantly different from that of Equation

2.27. However, the turbidity at 420 nm had decreased from

38.0 to 76.8% indicating that the main cause of opacity

in solutions was not Alginate material.

2.4.2 Light Scattering

The method of clarification of the polymer solutions proved to be critical with respect to the results obtained. Solutions that were not sufficiently clarified gave rise to anomalous results and dissymmetry, quantified by the dissymmetric ratio $Z_{45^0, 135^0}$:

$$Z_{45^0, 135^0} = \frac{I_{45^0} - I_{0,45^0}}{I_{135^0} - I_{0,135^0}} \qquad\qquad 2.28$$

where I_{45^0} and I_{135^0} = Intensities of light scattered by the sample solution at 45^0 and 135^0 respectively.

$I_{0,45^0}$ and $I_{0,135^0}$ = Intensities of light scattered by solvent at 45^0 and 135^0 respectively.

Table 2.6 shows the reduction in values of $Z_{45^0, 135^0}$ towards unity as centrifugation is increased from 3,000 to 100,000 x g.

Table 2.6 Dissymmetric Ratios, $Z_{45^0, 135^0}$ of Alginate Solutions

Centrifugation					
3,000 x g 2 hr.		25,000 x g 2 hr.		100,000 x g 2 hr.	
$c(g\ dl^{-1})$	$Z_{45,135^\circ}$	$c(g\ dl^{-1})$	$Z_{45,135^\circ}$	$c(g\ dl^{-1})$	$Z_{45,135^\circ}$
0.10	2.36	0.04	1.52	0.376	0.97
0.15	4.99	0.10	1.22	0.696	1.05
0.23	3.54	0.16	1.23	0.906	1.03
0.32	3.52	0.20	1.15	1.182	1.16
0.46	3.49			1.674	1.17

Although the method of Zimm (121) provides the most accurate

graphical analysis of light scattering data, significant

dissymmetry disrupts such a plot. This is the case for

solutions centrifuged at 3000 and 25,000 x g. It may,

however, be possible to use the data for light scattered at

90^0 only by applying Equation 3.29 (122).

$$\frac{Kc}{R_{90^0}} = \frac{1}{M_w} + 2Bc \qquad\qquad 2.29$$

In this way, M_w and the second virial coefficient, B, may

be obtained, but the radius of gyration cannot. Figure 2.4.

shows plots of $c/\alpha\ I_{90^0}$ against c for solutions centrifuged

at 3000 and 25,000 x g respectively. $c/\alpha I_{90^0}$ is related

to Kc/R_θ by Equations 2.17 and 2.13.

The values for solutions centrifuged at 3000 x g, see Table

2.7., do not give a linear relationship and extrapolation to

zero concentration is not feasible. In contrast, 25,000 x g

was sufficient to provide a linear plot with at least mean

square correlation coefficient of 0.9986; M_w = 20,600 $\pm$

1,000 g mol^{-1} and B = 9.03 $\pm$ 1.17 x 10^{-3} mol $cm^3 g^{-2}$.

The data is shown in Table 2.8.

Figure 2.4. The Effect of Alginate Concentration and Centrifugation on the Intensity of Light Scattered at 90°.

Centrifugation of Solutions : 3000 x g for 2 hr. ○,
25000 x g for 2 hr. ●.

y-axis: Intensity of Light Scattered at 90° $^{c}/_{\alpha I_{90°}}$ (x 10^{6})

x-axis: Alginate Concentration c(x 10^{3} g cm^{-3})
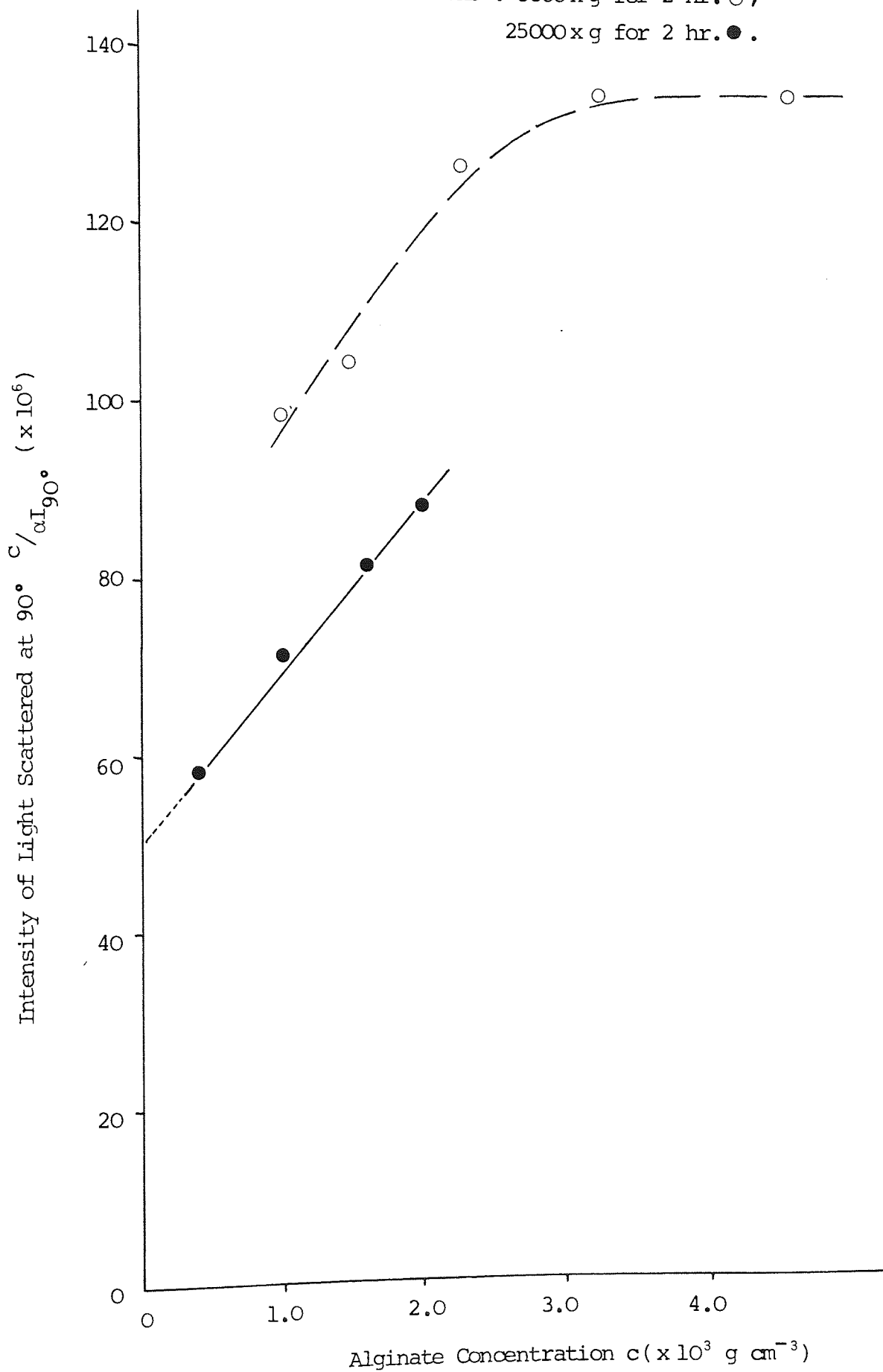
Table 2.7 Light scattered at 90^0 for solutions centrifuged at 3000 x g for 2 hr.

I_θ (divs)	$c/\alpha I_\theta \times 10^6$	c (g dl^{-1})
10.14	98.60	0.100
13.98	104.4	0.146
17.88	127.5	0.228
23.98	135.1	0.324
33.78	134.7	0.455

Table 2.8 Light scattered at 90^0 for solutions centrifuged at 25,000 x g for 2 hr.

I_θ (divs)	$c/\alpha I_\theta \times 10^6$	c (g dl^{-1})
6.85	58.39	0.04
14.00	71.43	0.10
19.60	81.63	0.16
22.40	89.29	0.20

Values of the refractive index increment dn/dc were obtained

after calibration of the differential refractometer with

sodium chloride solutions The instrumental constant k' =

was equal to $0.9434 \times 10^{-3} \text{div}^{-1}$.

Alginate solutions tested before and after ultracentrifugation

gave dn/dc values of 0.171 ± 0.002 and 0.138 ± 0.014 $\text{cm}^3 \text{g}^{-1}$

respectively. The plots of the refraction distance, d, against

c are given in Figure 2.5.. These values compare favourably

with dn/dc of Alginate in 0.1 N NaCl due to previous workers

Buchner et al (16) obtained 0.165 $\text{cm}^3 \text{g}^{-1}$;

Haug and Smidsrød (53) 0.157 $\text{cm}^3 \text{g}^{-1}$, Brucker et al (55) 0,180,

0.153 and 0.168 $\text{cm}^3 \text{g}^{-1}$ for unfractionated, G-rich and M-rich

Alginates respectively; Mackie et al (56) 0.154 $\text{cm}^3 \text{g}^{-1}$

irrespective of M/G ratio.

There appears to be a significant difference between dn/dc

before and after ultracentrifugation, which may have been due

to the presence of contaminant plant material. In fact, Haug

and Smidsrød (53) examined the light scattering properties

of non-clarified Alginate solutions and concluded that

spherical and ellipsoid particles were present, and assumed

them to be of plant origin.

Scott et al (115) studied the light scattering of Sodium

Alginate using a Photo-Gonio Diffusometer instrument and they

failed to obtain Zimm plots capable of providing $(R_G^2)^{\frac{1}{2}}$

and B values after centrifugation at 35,000 x g for 1 hr.

Figure 2.5. Determination of the Refractive Index
Increment, dn/dc from a plot of Refractive Index
Difference against Alginate Concentration.

Before Centrifugation ● and After Centrifugation ○

Figure 2.5 (see facing page).

$\frac{dn}{dc} = 0.171 \pm 0.002 \ cm^3 g^{-1}$

$\frac{dn}{dc} = 0.138 \pm 0.014 \ cm^3 g^{-1}$

Refractive Index Difference Δn (x 10^3)

Alginate Concentration c(g dl^{-1})
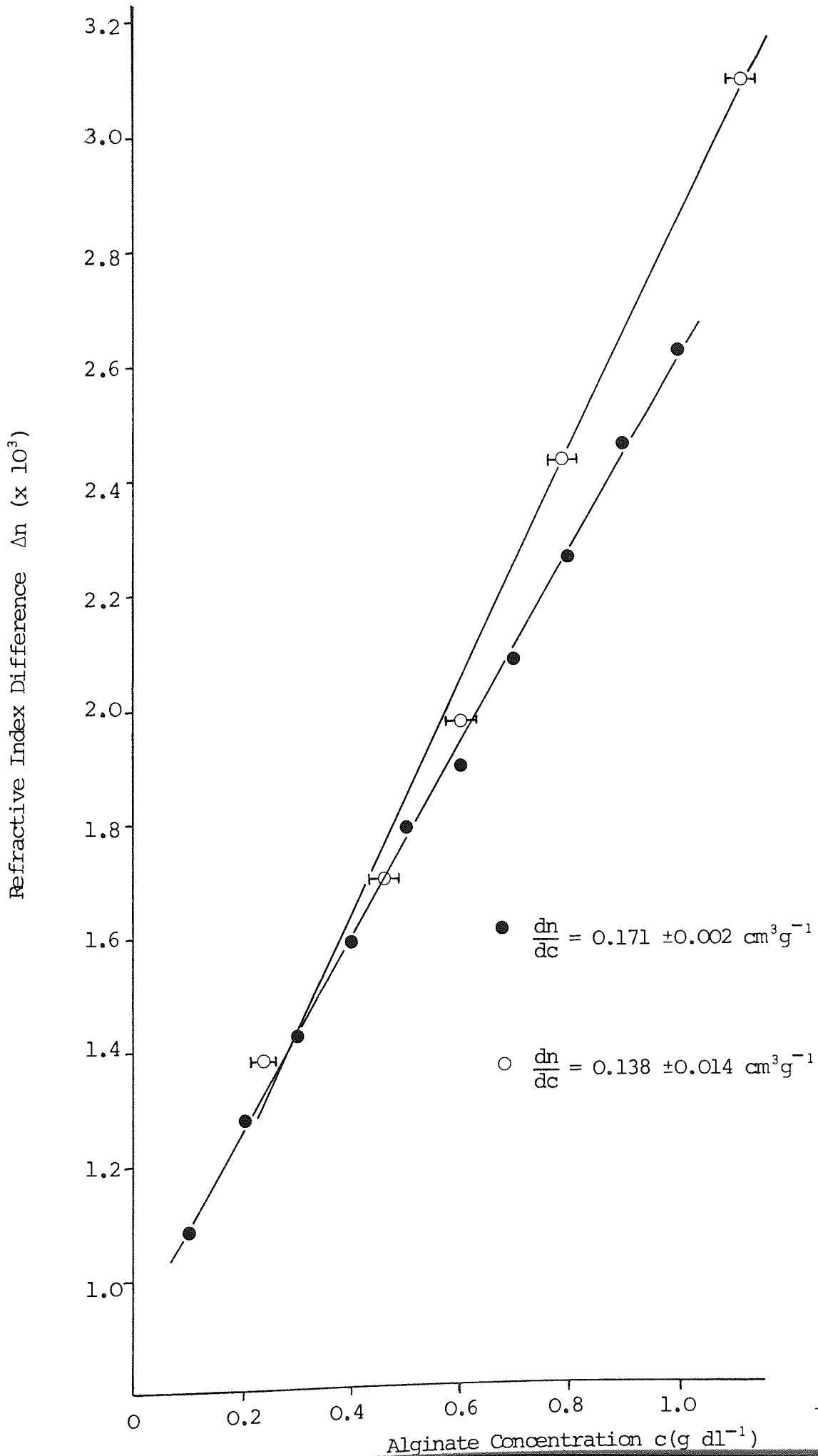
Using pectin solutions, Cohen and Eisenberg (123) found

considerable dissymmetry in their Zimm plot following

centrifugation at 32,000 x g for 15 hr. This was blamed on

the presence of aggregates. Further, Holt et al (124)

described the aggregates as microgel and showed the usefulness

of ultracentrifugation in reducing the downward curvature of

the Zimm plot which occurs at low angles. The fact that the

molecular weight may be reduced by ultracentrifugation itself

is inevitable but under specified conditions, the technique

is still valid.

For the Alginate solutions centrifuged at 100,000 x g for

2 hr., a Zimm plot was constructed with k = 20, as shown in

Figure 2.6. The corresponding data is detailed in Table 2.9..

The values of the derived parameters were

M_W = 22,500 $\pm$ 2000 g mol^{-1} ; $(R_G^2)^{\frac{1}{2}}$ = 66.8 $\pm$ 6.7 nm;

B = 2.11 $\pm$ 0.21 x 10^{-3} mol cm^3 g^{-1} . These values compare

favourably with those of previous studies (17,20).

2.4.3 Continuous Shear Rheometry

By subjecting the Alginate solutions to a wide range of shear

rates and measuring the resultant shear stress, it is possible

to observe the onset of non-Newtonian behaviour. The shear

thinning which occurs due to some ordering and rotation of the

molecules is important in relating the dilute solution

behaviour to the bulk properties of the polymer (78,125). The

flow-curves given in Figures 2.7 to 2.9 show that derivations

from Newtonian behaviour are seen at concentrations in excess

Figure 2.6. Zimm Plot for Alginate Solutions Ultracentrifuged at 100,000 x g for 2 hr.
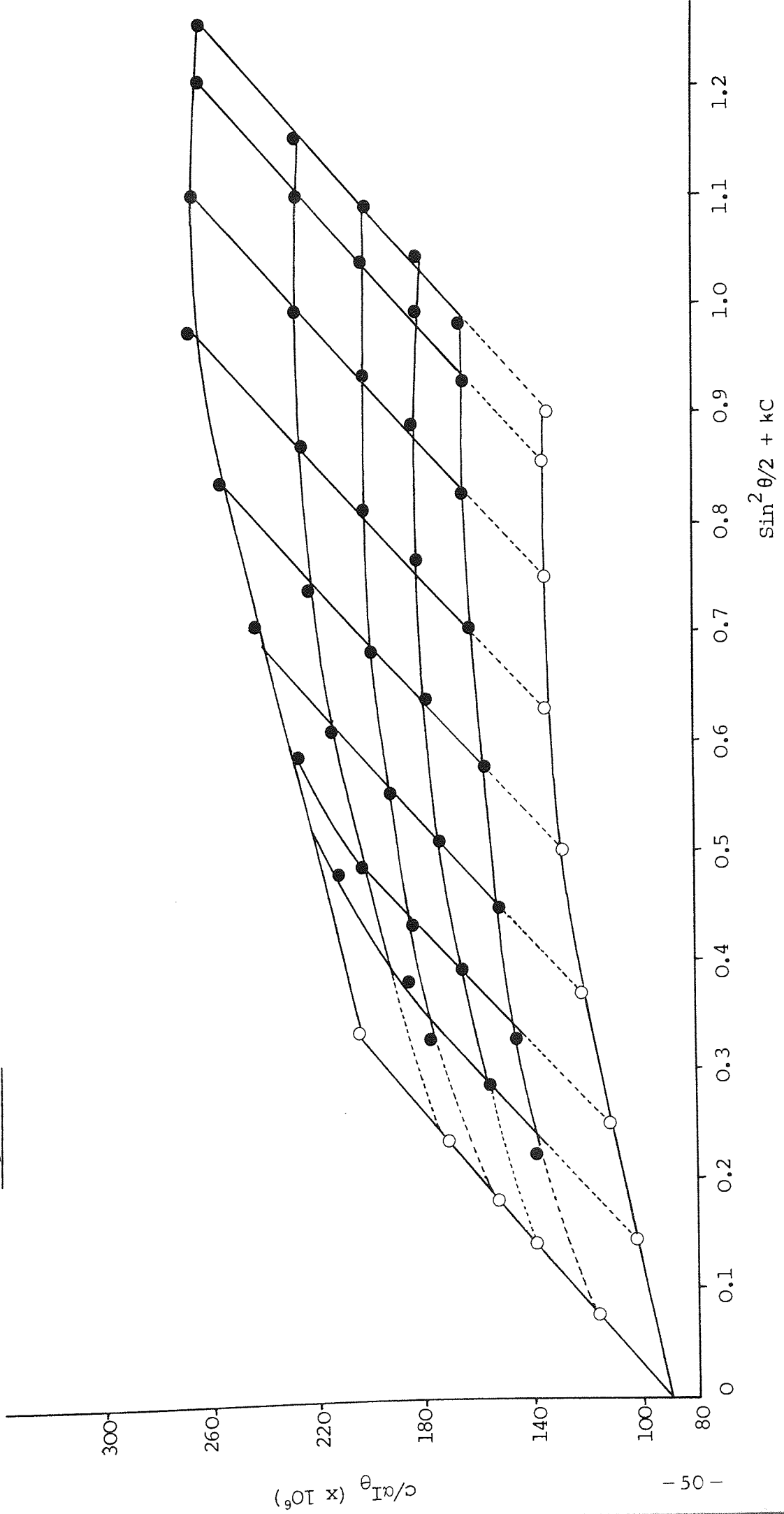
Table 2.9 Light Scattering Data for Solutions Ultracentrifuged at 100,000 x g for 2 hr.

Angle (deg)	Concentration ($\times 10$ g cm^{-3})											
	0.0		3.76		6.96		9.06		11.82		16.74	
	y*	x†	y	x	y	x	y	x	y	x	y	x
0	90.0	0.0	116.0	0.075	139.0	0.139	152.0	0.181	171.0	0.236	205.0	0.335
45	102.0	0.146	138.4	0.221	156.1	0.285	178.6	0.327	184.9	0.382	212.5	0.481
60	111.0	0.250	145.5	0.325	165.5	0.389	184.4	0.431	204.6	0.486	227.9	0.585
75	121.0	0.371	151.8	0.446	174.7	0.510	193.6	0.552	215.8	0.607	244.9	0.706
90	128.0	0.500	157.0	0.675	178.9	0.639	201.3	0.681	224.7	0.736	257.9	0.835
105	134.0	0.629	162.0	0.704	182.6	0.768	202.2	0.810	227.1	0.865	269.6	0.964
120	135.0	0.750	164.9	0.825	183.7	0.889	203.1	0.931	229.6	0.986	267.0	1.085
135	135.0	0.854	165.1	0.929	182.3	0.993	203.2	1.035	228.4	1.090	263.0	1.190
142.5	133.0	0.902	166.6	0.977	182.1	1.041	201.6	1.083	228.8	1.140	264.0	1.240

* $y = c/\alpha I_\theta \times 10^6$

† $x = Sin^2\theta/2 + kc$ where $k = 20$

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Figure 2.7. Continuous Shear $\tau(\dot\gamma)$ Flow-Curves for various Concentrations of Sodium Alginate Solutions. Concentrations (g dl^{-1}) : 0.25 △ ,0.5 ▲ ,0.75 ○ ,1.0 ◐, 1.5 ◑ ,2.0 ●.
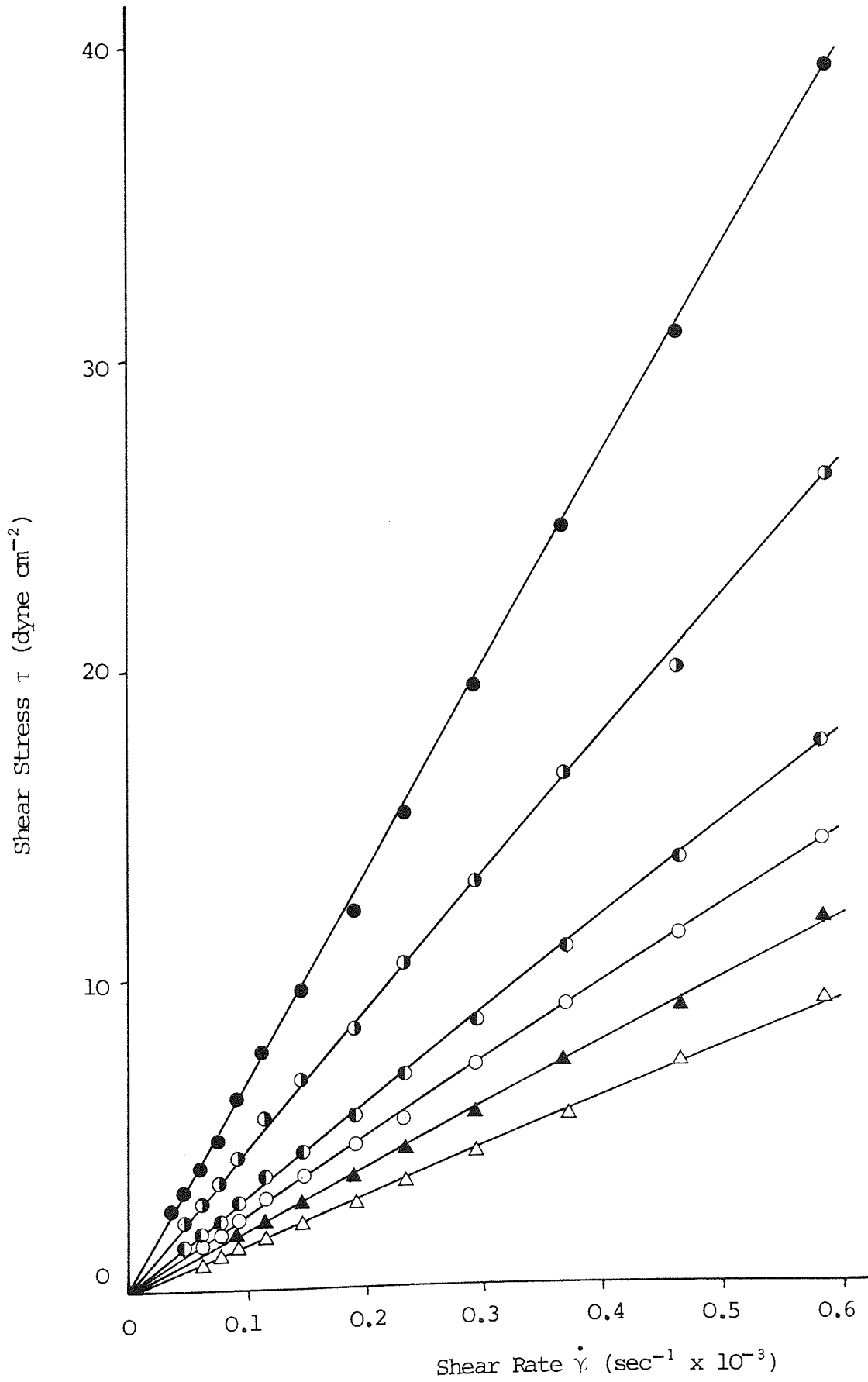
Figure 2.8. Continuous Shear $\tau(\dot{\gamma})$ Flow-Curves for Various Concentrations of Sodium Alginate Solutions. Concentrations (g dl^{-1}): 3.0 ○,4.0 ◐,5.0 ◑,6.0 ●.
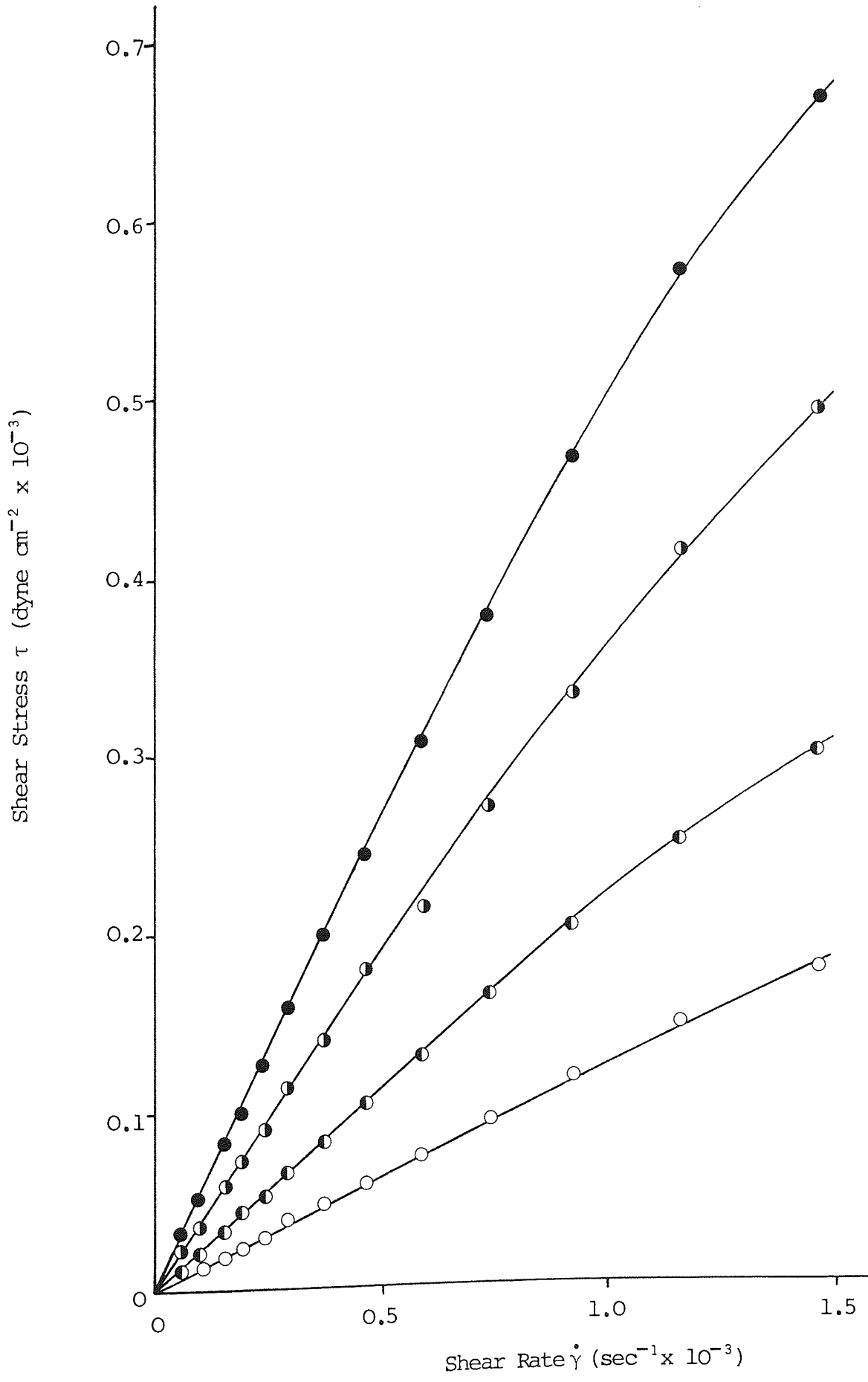
Figure 2.9. Continuous Shear τ ($\dot{\gamma}$) Flow-Curves for Various Concentrations of Sodium Alginate Solutions. Concentrations (g dl^{-1}) : 7.0 ◯, 8.0 ◑, 9.0 ◑, 10.0 ●.
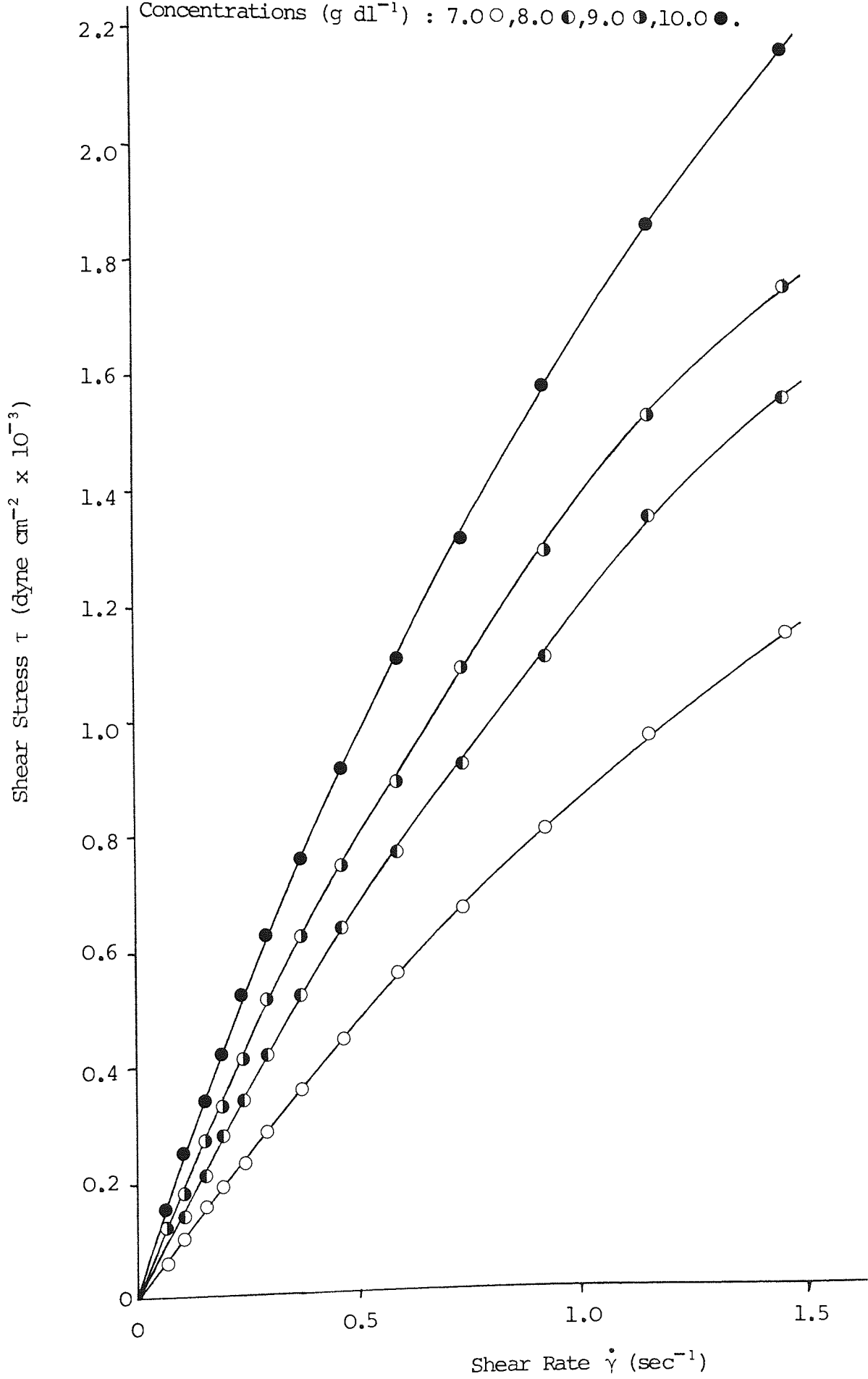
of about 6 g dl^{-1}. This was not due to any spurious effects
such as expulsion of the sample from the gap since apparent
shear thinning was absent in lower concentrations.

The reproducibility of the cone and plate system for
measuring viscosity was demonstrated using (a) Silicone Fluid
100 cs. and (b) Sodium Alginate 5 g dl^{-1} solution. The results
were (a) $\eta = 1.091 \pm 0.014$ poise (n = 8) and (b) $\eta = 0.353 \pm$
0.017 poise (n = 10), showing that more reproducible results
were obtained using a pure Newtonian liquid, probably due to
its homogeneity.

The Newtonian viscosities, ie, apparent viscosities calculated
at low shear rates and approximating to zero shear viscosities,
are given in Table 2.10. The relationship with concentration
can be described by Equation 2.30. Equations of this type
were suggested by McDowell (1).

$$\log_{10} \eta \ = \ 0.858 \ c^{\frac{1}{2}} \ - \ 2.43 \qquad\qquad 2.30$$

The line is illustrated in Figure 2.10 where the least mean
square correlation coefficient $r = 0.9983$.

Figure 2.10. The Effect of the Concentration of
Alginate on Newtonian Viscosity.
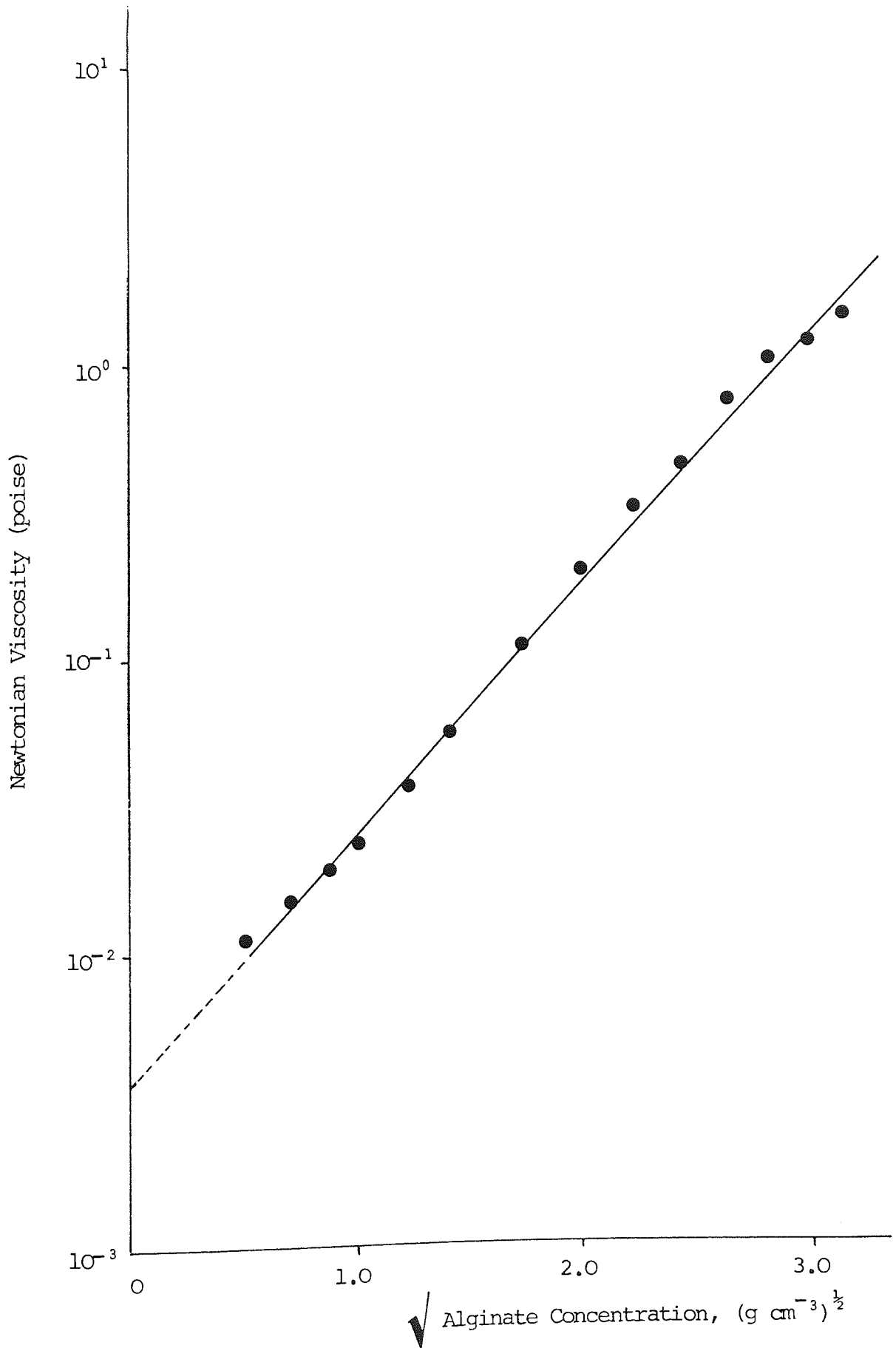
Table 2.10 Newtonian Viscosities of Sodium Alginate
Solutions at 20^0C.

Concentration (g dl^{-1})	Viscosity (poise)
0.0	0.0090
0.25	0.0115
0.5	0.0152
0.75	0.0193
1.0	0.0242
1.5	0.0377
2.0	0.0578
3.0	0.115
4.0	0.205
5.0	0.343
6.0	0.478
7.0	0.814
8.0	1.13
9.0	1.29
10.0	1.59

2.4.4 <u>Oscillatory Shear Rheometry</u>

The (ν, ω) and (C, ω) curves for two Newtownian liquids

shown in Figures 2.11 and 2.12. give the expected results,

namely that ν = 1 and C = 0 when ω = ω_0. The value of ω_0 for

the size 7 torsion bar was 25.1 rad s^{-1}. The viscoelastic

determinations for Carbopol 941 1.0 g 100g^{-1} detailed in

Table 2.11 are in good agreement with the results of Barry

and Meyer (82) showing that viscoelastic measurements were

comparable. The amplitude used for these measurements was

28.1 x 10^{-4} rad. which compares with 31 x 10^{-4} rad. used by

Barry and Meyer (119), therefore the collation is unaffected

by any non-linear viscoelastic effects.

Figures 2.13. and 2.14. illustrate the oscillatory data for

Figure 2.11. The Effect of the Frequency
on (a) the Amplitude Ratio and (b) the Pha
Silicone Fluid 100 cs.

Figure 2.11 (see facing page).
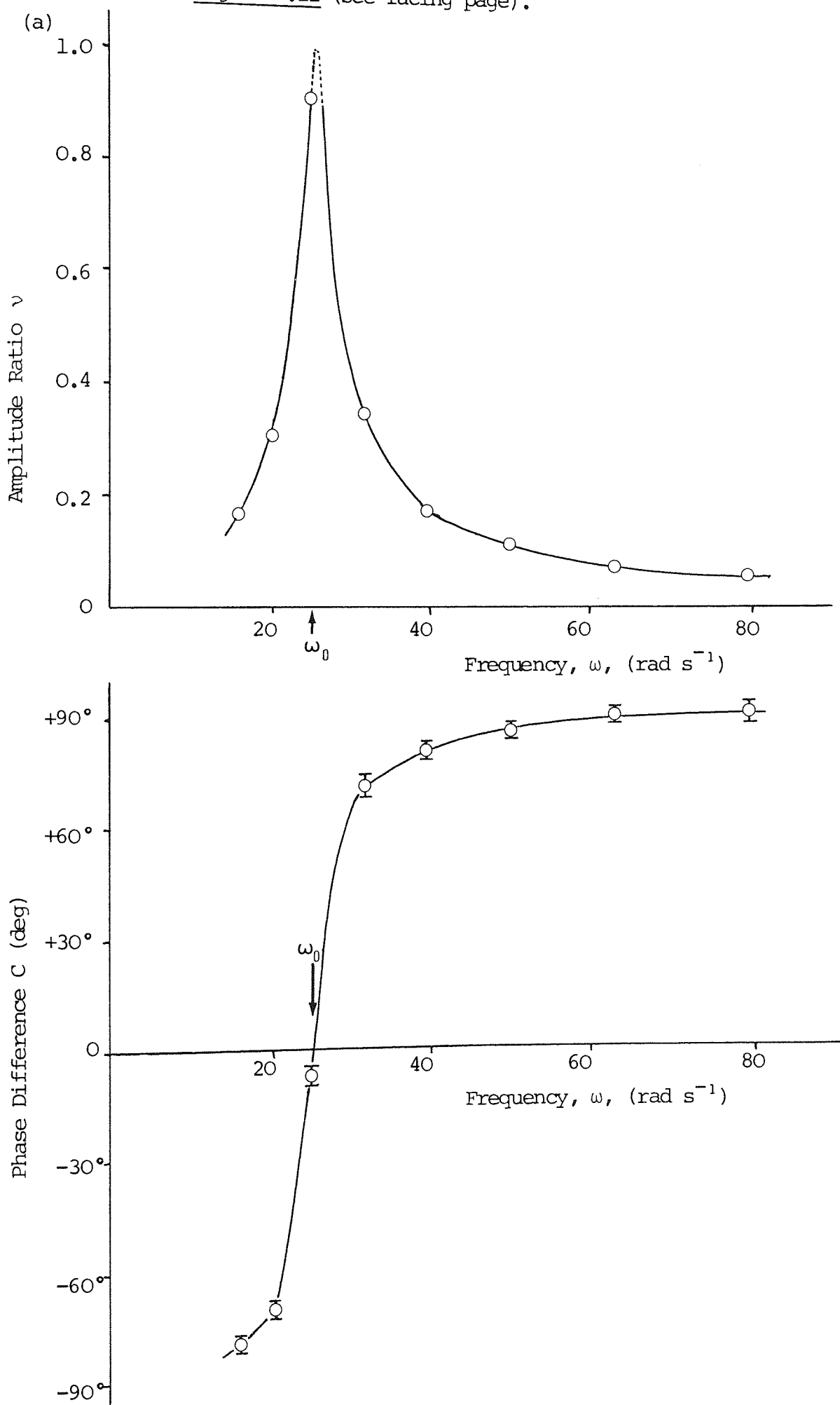
Figure 2.12. The Effect of the Frequency of C
on (a) the Amplitude Ratio and (b) the Phase L
Liquid Paraffin B.P.

Figure 2.12 (see facing page)

A.

Amplitude Ratio, ν.

ω_0

Frequency ω (rad s^{-1})

B.

Phase Difference C (deg).

ω_0

Frequency ω (rad s^{-1})
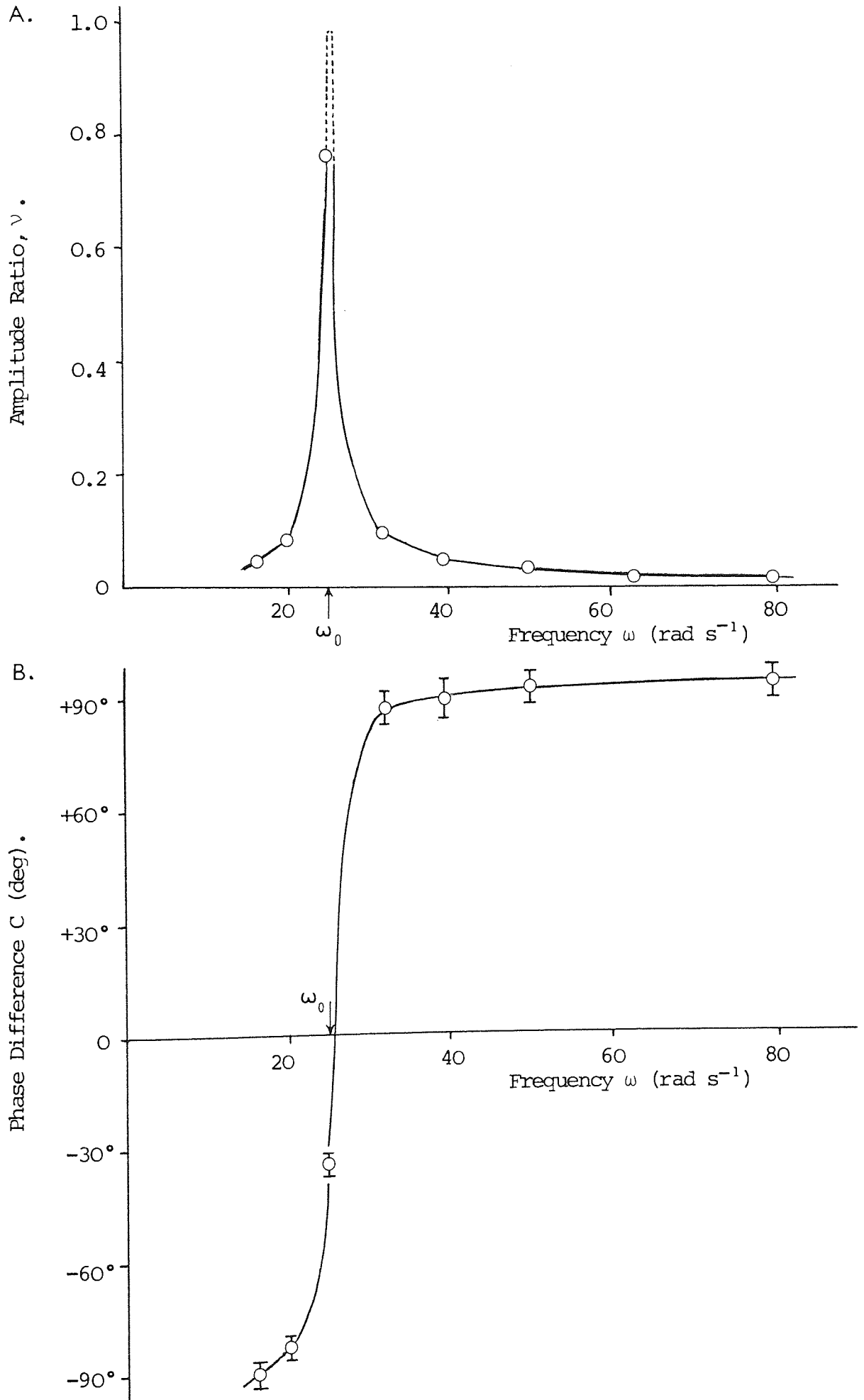
Figure 2.13. The Effect of the Concentration of Sodium Alginate Solution on the Storage Modulus, G', plotted as a function of the Frequency of Oscillation.

Concentrations (% w/w) : 5.1 ○,10.0 ◉,12.7 ◑,15.0 ●,
17.8 △,19.8 ▲.

Figure 2.13 (see facing page)

Storage Modulus G' (dyne cm^{-2})

Frequency ω (rad s^{-1})
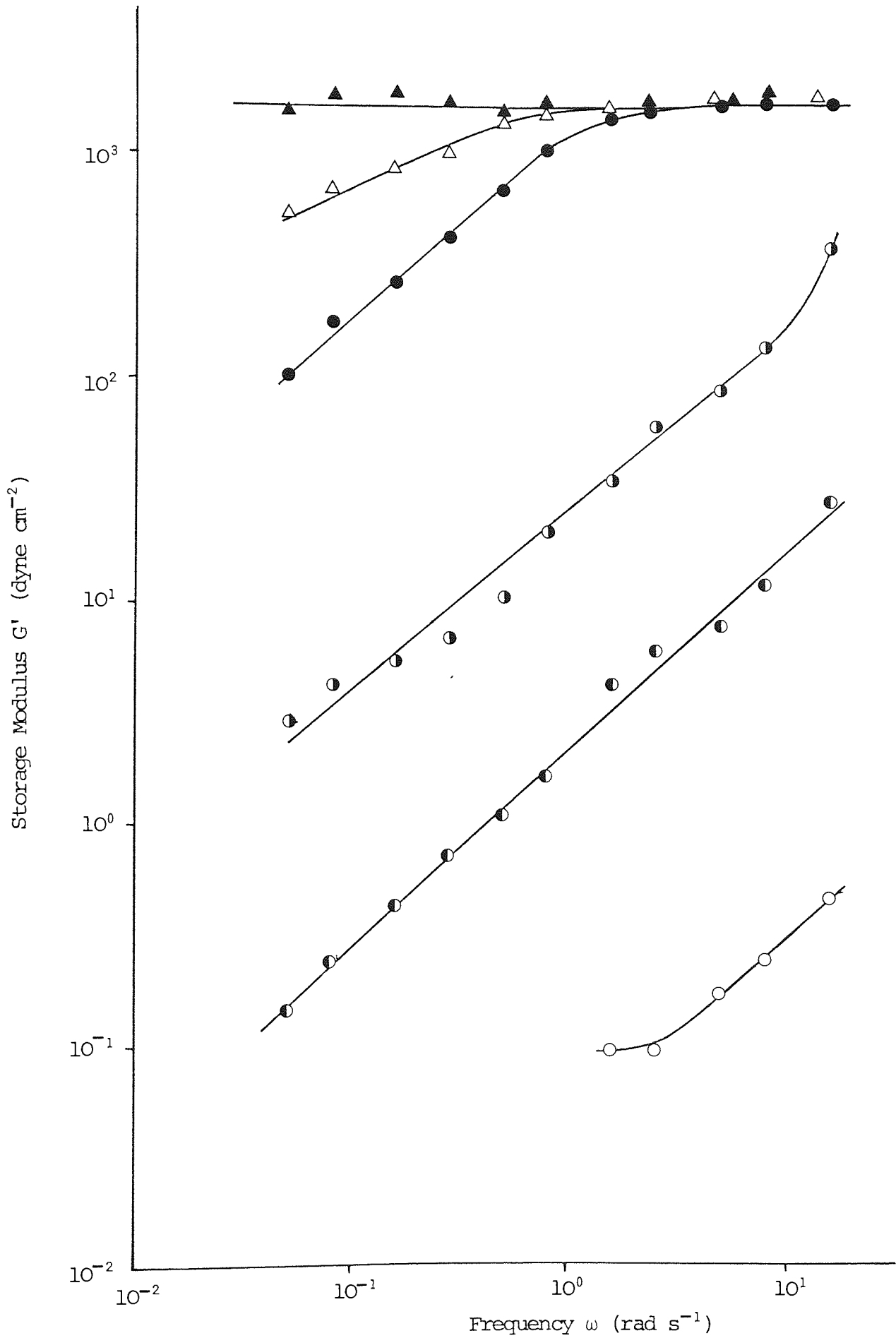
Figure 2.14. The Effect of the Concentration of Sodium Alginate Solution on the Dynamic Viscosity, η, plotted as a function of the Frequency of Oscillation.

Concentration (% w/w) : 5.1△,8.2○,10.0◐,
12.7◑,15.0●.

Frequency ω (rad s^{-1})
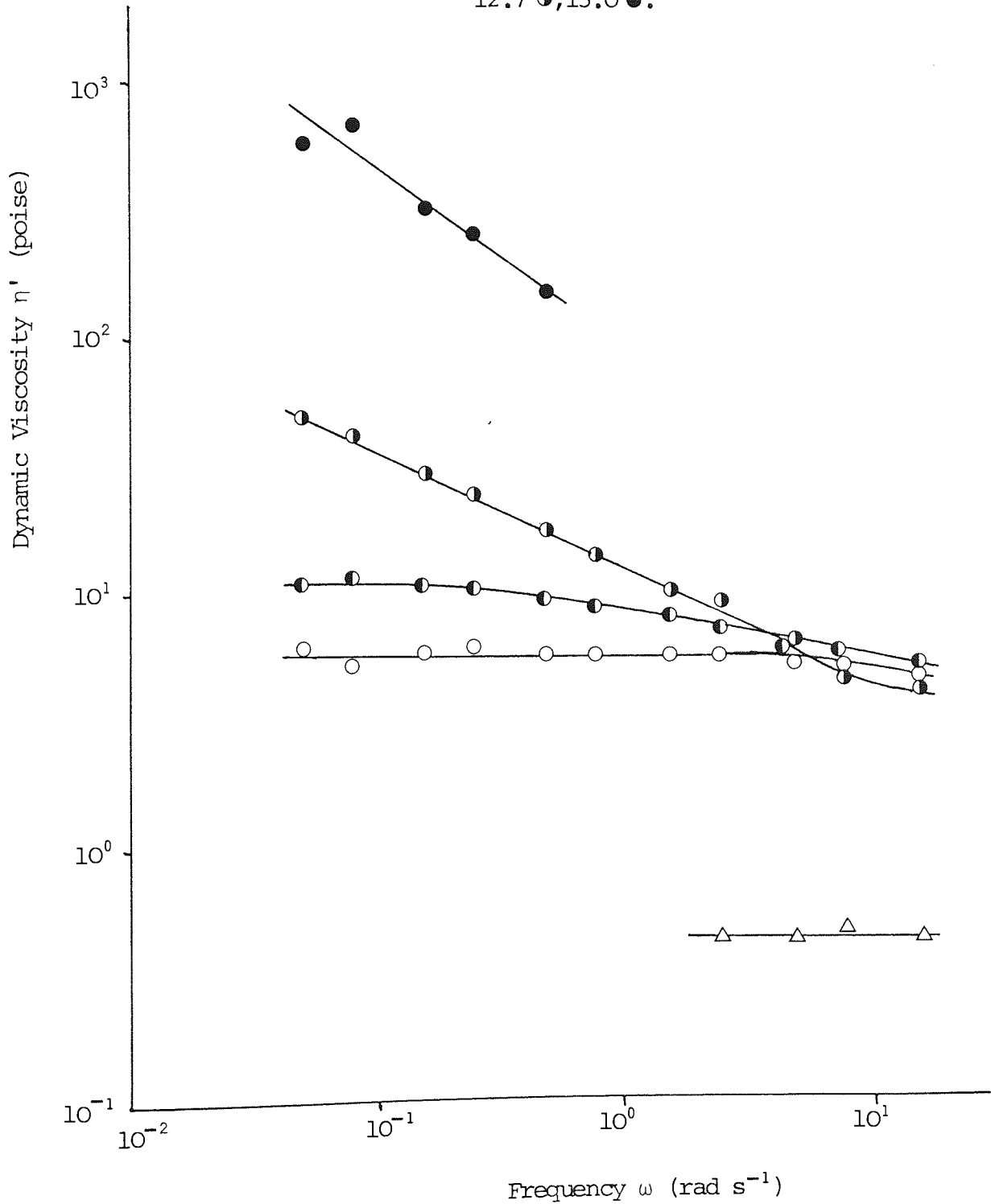
Sodium Alginate solutions in terms of $G'(\omega)$ and $\eta'(\omega)$ respectively. The incomplete curves for 5.1 g dl^{-1} Alginate occurred because the measuring system was not sufficiently sensitive to distinguish the output amplitude from background movements caused by air convection currents. On the other hand, properties and therefore $\eta'(\omega)$ values depend on the accurate measurement of small phase angles. As would be expected, the phase angle becomes smaller as the frequency is increased until eventually, accurate $\eta'(\omega)$ values are no longer obtained.

Table 2.11   Viscoelastic Data for Carbopol 941 1.0 g 100 g^{-1} measured at 28.1 x 10^{-4} rad. amplitude.

Frequency, ω (rad s^{-1})	Storage Modulus, G' (dyne cm^{-2})	Dynamic Viscosity, η' (poise)
0.0497	210	-
0.0792	218	-
0.157	227	-
0.249	235	-
0.497	247	78.4
0.792	253	58.0
1.57	262	40.1
2.49	272	24.9
4.97	295	12.6

The $\eta'(\omega)$ curves suggest that viscoelastic behaviour commences at approximately 10 g dl^{-1} concentration whereas the $G'(\omega)$ curves show a small elastic contribution in a 5 g dl^{-1}

solution. At 20 g dl^{-1} Alginate, the solution was completely elastic within the frequency range measured. However, the fact that the solution would still flow under gravity suggested that the frequencies used were much higher that the retardation time of the material and therefore the viscosity may only be measured at lower frequencies.

2.5 <u>Discussion</u>

Several studies have been published on the properties of Alginate either at the molecular level (5,15,16,20,46-50,52-56) or in bulk solutions (1,126,127) but rarely have the two aspects been investigated simultaneously. Such information would be potentially useful for choosing bulk properties of a system from a knowledge of the molecule. Rees (22,128,129) and Morris (130,131) have studied polysaccharides in solution using techniques such as circular dichroism, optical rotation, and nuclear magnetic resonance from which it was possible to make qualitative conclusions on conformation and solute-solute interactions. However, any attempt to unite the two fields of molecular and bulk properties falls short of its goal because of the lack of theoretical knowledge. For example, Franks (132) succeeded in showing only tentative links between optical rotation measurements, second virial coefficients, and 'Monte Carlo' <u>ab initio</u> calculations of molecular conformation for carbohydrates.

Nevertheless, even without such an exhaustive knowledge of the polysaccharide under study, it is useful to characterise

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the material in terms of both molecular and bulk parameters

for dilute and concentrated solutions (133).

It can be seen from the molecular data for $(R_G^2)^{\frac{1}{2}}$,

M_w and $[\eta]$, that the Flory Equation (see Equation 2.4) can be

be used to calculate Φ. ie., $\Phi = 0.544 \times 10^{21}$.

Equation 2.18 was used to convert the radius of gyration,

$(R_G^2)^{\frac{1}{2}}$, to the root-mean-square end-to-end distance, $(\overline{r}^2)^{\frac{1}{2}}$

By consulting the tabulated values of $\Phi(\varepsilon)$ according to

Bloomfield and Zimn, (79) the lowest $\Phi(\varepsilon)$ values given are

0.686 and 0.422 x 10^{21} for straight- and ring-chain polymers

respectively. In this case, $\varepsilon = 0.5$ and therefore the

exponent α in the modified Staudinger Equation (see Equation

2.2) is equal to 1.25. This high value of α is indicative of

a very stiffly coiled molecule and is in contrast to the value

of 1.0 derived by Smidsrød (52). Because of the nature of the

exponential term, small differences in α lead to large

differences in M_η. If $\alpha = 1.25$ is arbitrarily substituted

for $\alpha = 1.0$ in Smidsrød's equation, we obtain $M_\eta = 6000$ g

mol^{-1}. Therefore, the most appropriate equation for Protonal

LFR5/60 Sodium Alginate is $[\eta] = 3.8 \times 10^{-6} M_w^{1.25}$. However,

it should be noted that M_η is equivalent to M_w only when

$\alpha = 1.0$ (62).

The relationship between two variables can always be written

as an exponential rule if the range of applicability is

limited. Hence, the range of Smidsrød's Equation has been

exceeded by substituting $[\eta] = 1.056$ dl g^{-1} and a separate

calibration would be required for the low molecular weight Protonal LFR5/60.

The value of A_m, the Kuhn statistical segment from light scattering data using Equation 2.17., was 452 nm. This compares favourably with $A_m = 390$ nm at $\mu = 0.1$ due to Smidsrød [20] obtained from viscosity data using the Bloomfield-Zimm theory for the Flory Equation to obtain $(\overline{r^2})^{\frac{1}{2}}$ Comparisons such as this substantiate the absolute value of M_W obtained as well as providing an indication of the relative extension of the molecule.

The hydrodynamic characteristics are of most interest with respect to the rheological properties of Alginate solutions. A free draining molecule would provide a lower frictional resistance in flow than would a non-draining molecule of the Flory 'equivalent sphere' theory. The free draining behaviour seen in rigid chain molecules in good solvents and non-draining behaviour of very flexible chains in poor solvents, are two extremes and most molecules are probably best described in terms of partial free drainage. However, only the behaviour of the two extremes has been quantified. Both the Kirkwood-Riseman [78,125] and the Debye and Bueche [134,135] theories attempt to quantify the fractional coefficient of free-draining molecules. The theory of Rouse [136] goes further and is based on a bead-spring molecular model whereby the energy storage and dissipation in sinusoidally oscillating displacements, are calculated; from this, the complex modulus or the complex

viscosity is calculated (60).

The theory attributed to Zimm (137) deals with non-draining
molecules whereby frictional resistance is considered to
include the viscous drag due to hydrodynamic interactions.
Under conditions of diminishing viscous drag within a molecule,
the Zimm theory reduces to the Rouse theory (138).

In conclusion, it can be seen that the Sodium Alginate molecule
under study is of a low molecular weight and does not show any
extreme deviations from Newtonian behaviour in solution. The
molecular parameters determined agree well with previously
published data. At high polymer concentrations, in excess of
about 15 g dl^{-1} , entanglements are sufficient to lead to
dominant elastic behaviour over and above the viscous
properties.

3. RHEOLOGICAL PROPERTIES OF SUSPENDING AGENTS

3.1 Introduction

The most frequently used and the simplest method of suspending drug particles in a liquid medium is by the use of thickening agents. These may be dispersed, for example, sodium montmorillonite and bentonite, or dissolved as is the case for polyelectrolytes for example. The formulation of pharmaceutical suspensions, in contrast to formulation in other industrial products is limited in its choice of suspending agent by toxicological and regulatory restraints. This demands a good working knowledge of the agents available.

The most useful methods for assessing suspending agent performance are sedimentation and rheological testing. Many studies have been published in the general rheological (eg. 100,139-142) and pharmaceutical (eg.143,144) literature on the flow behaviour of systems with particles dispersed in non-Newtonian polymer solutions. When the volume fraction of particles, $\phi < 0.05$ (139) then the rheological properties are primarily those of the suspending agent alone. For this reason, many studies have characterised the behaviour of such agents as 'Carbopol' (144,146-148) and Xanthan Gum (149-152). Few studies have appeared in the pharmaceutical or allied literature (153-155) which consider the rheological aspects of combining two different suspending agents; such a process may be deemed necessary in order to obtain a certain rheological 'profile', or for pharmacological reasons.

In this study, the polyelectrolyte suspending agents Xanthan gum and Carbopol 934P were investigated with respect to their rheological properties in the presence of Sodium Alginate. For therapeutic reasons, outlined in Section 1.3., a low molecular weight Sodium Alginate is present in the formulation under study. The viscosity of the Alginate alone is insufficient to suspend the required particles for the desired length of time and a further agent is necessary.

In general, the conformation of a polyelectrolyte chain is usually disturbed by the presence of another polyelectrolyte, resulting in an antagonistic effect. Therefore, in suspension formulation, higher concentrations of combined suspending agents would be necessary.

Interactions between polyelectrolytes are usually of an ionic nature (156) although specific binding mechanisms have been noted in certain cases (157,158). In the present study, the combinations of 'Carbopol' - Sodium Alginate and Xanthan gum - Sodium Alginate were investigated for the effects of concentration, storage, shearing and the method of measurement on the rheological parameters obtained.

Two types of rheological testing were carried out, namely continuous shear and oscillatory methods. By comparing the results obtained using the two techniques, it may be possible to pinpoint certain characteristics in the continuous shear rheograms which are normally only quantified using a more

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elaborate technique, eg. oscillatory testing.

Finally, in order to illustrate the applicability of oscillatory shear measurements to formulated products, some proprietary oral liquid preparations were tested. The proposal by Davis (151) that tan δ (ω) curves could be used as "fingerprints" for individual preparations will be discussed.

3.2 <u>Theory</u>

The rheological methods used in this work involved oscillatory and continuous shear techniques. The reader is referred to Section 2.2.3 for the theoretical basis of these methods.

3.2.1 <u>Xanthan Gum and Carbopol</u>

Xanthan gum is an extracellular polysaccharide produced by <u>Xanthomonas campestris</u>. It has a cellulose backbone with trisaccharide side chains on alternate residues as shown in Figure 3.1. according to Jansson <u>et</u> <u>al</u> (159). A pyruvate moiety is attached to approximately half of the terminal mannose units of the side chain, (160). The molecular weight of 'Keltrol' [1] has been estimated to be 1.0×10^{7} (152) and 1.75×10^{6} g mol^{-1} (161), so it is likely that polydispersity is high. The wide use of Xanthan gum stems from its excellent stability over a wide range of pH, temperature, and ionic strength, and also its remarkable viscosity reduction on shearing, (149). 'Carbopol' [2] is a synthetic poly (acrylic acid) cross-linked with polyalkyl ether (162), of general formula as given in Figure 3.2. Only one grade, Carbopol 934P,

[1] 'Keltrol' is a registered trademark of Kelco Co. for Xanthan Gum.
[2] 'Carbopol' is a registered trademark of B.F. Goodrich Co., Cleveland, Ohio, U.S.A.

Figure 3.1. The Structural Formula of Xanthan Gum.

Side chain:

β-D-Mannose-
(1,4)-β-D-Glucuronic acid-
(1,2)-α-D-Mannose-6-O-acetyl.

Pyruvate attached to approx.
50% of terminal Mannose units.
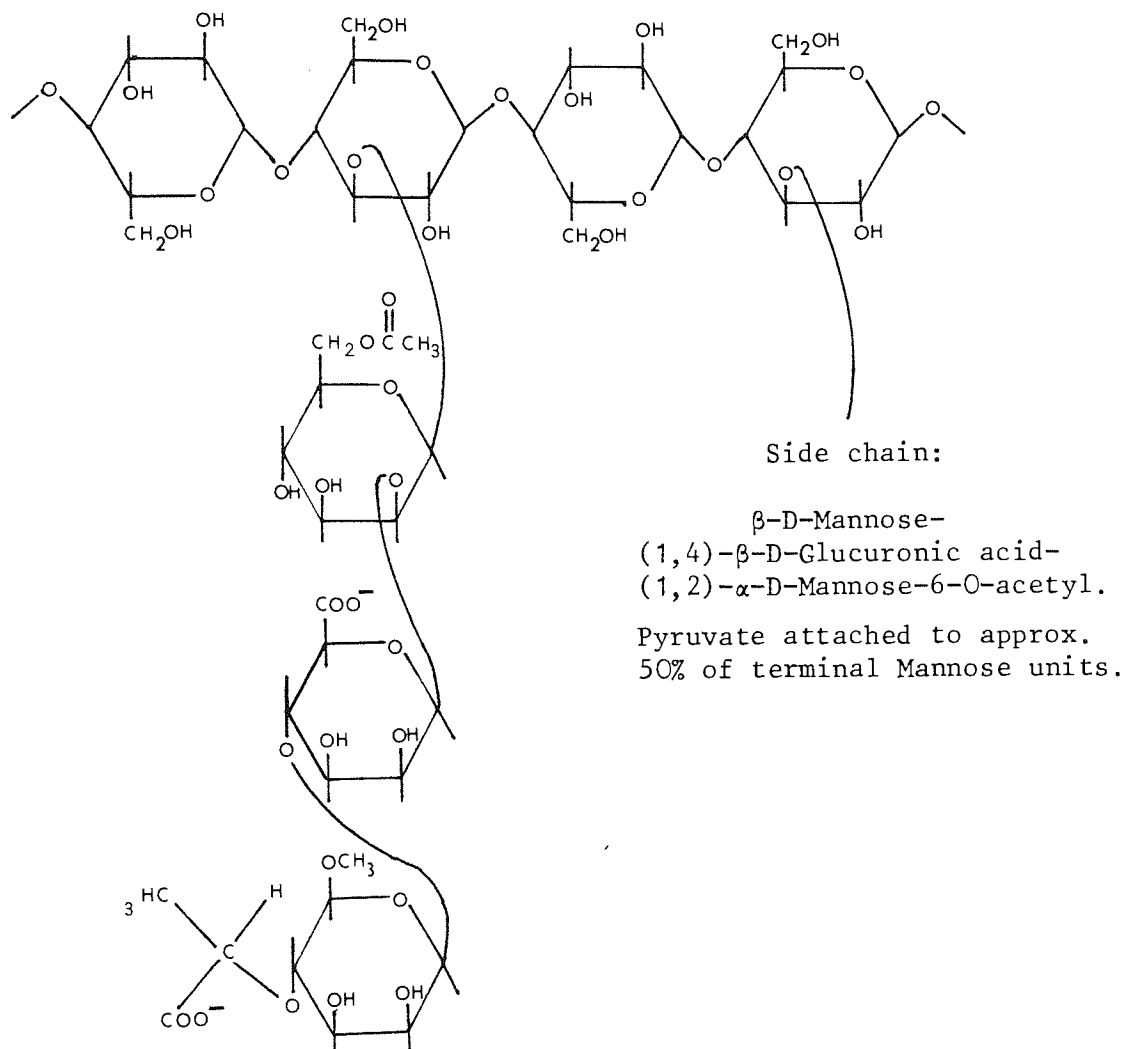
Figure 3.2. The Structural Formula of 'Carbopol'.

Polyether chain with
Polyalkenyl cross-linker
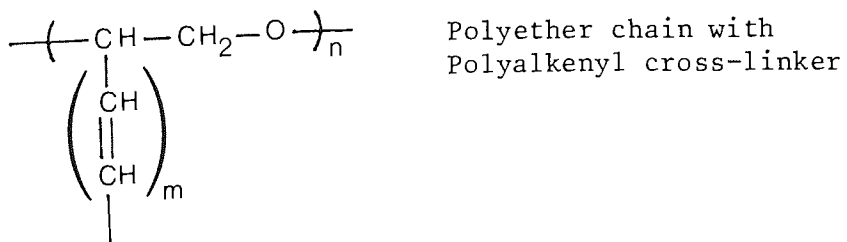
is suitable for use in pharmaceuticals, because of the presence
of vinyl monomers in other grades (163). Since Carbopol 934P
is a commercial product, it probably has high polydispersity
(148), which is reflected in the molecular weight determin-
ations of $22 \pm 3 \times 10^6$ (164) and 3.0×10^6 g mol^{-1} (165,166).
An equivalent weight of 73.5 g was determined by Testa and
Etter (164, 167) although 76 g is the more generally accepted
value (162), Carbopol is used widely because of its high
viscosity at low concentrations but it suffers from being
sensitive to ionic strength and to small deviations from
neutral pH.

3.2.2 Rheological Properties and Suspending Ability

There are three rheological parameters which have been
useful as indicators of suspending ability. First, and
at present highly favoured, is the zero shear viscosity,
η_0 , obtainable at very low shear rates or frequencies.
Buscall et al (40) showed the settling rates in non-Newtonian
media to be inversely proportional to η_0 . This is a sensible
result since the settling rates in Newtonian media as defined
by Stokes' Law, are inversely proportional to the media
viscosity. The second parameter is the instantaneous shear
modulus, G_0 , the reciprocal of the instantaneous compliance,
J_0 , from creep measurements. Its use has been suggested by
Strenge and Sonntag (41), and a theoretical justification for
using the shear modulus was provided by Goodwin and
Khidher (168). Thirdly, the yield value, τ_y , has frequently

been used in the past (169) but not without difficulty because of the problem of sharply defining the point at which flow commences, independently of the test method.

3.2.3 Shearing of Polymer Solutions

A decrease in apparent viscosity, η , with increasing shear rate, $\dot\gamma$, can occur as a result of either intra- or inter-molecular effects, (170), for dilute and concentrated solutions respectively. The terms 'dilute' and 'concentrated' are used with reference to the molecular weight. Shear thinning in dilute solutions leads to relatively small reductions in η, (171), but in concentrated solutions, η is frequently reduced by several orders of magnitude where viscosity is due to long relaxation times associated with entanglements. Rearrangement of entanglements takes place during shearing and Graessley [57] quantified this using a characteristic relaxation time, t_η = $1/\dot\gamma_\eta$ where $\dot\gamma_\eta$ is the shear rate at which non-Newtonian behaviour becomes apparent. The use of $\dot\gamma_\eta$ required that η_0 be known and for some high polymers, it may be difficult to perform experiments at sufficiently low $\dot\gamma$ to determine η_0. Values of $\dot\gamma_\eta$ of the order of 10^{-6} sec^{-1} are not unusual for suspending agent systems, (40).

3.2.4 Quantifying Non-Newtonian Flow

As mentioned in Section 2.2.3. many equations are available for quantifying the shear rate dependence of viscosity in non-Newtonian flow. Physical significance is frequently attached

to coefficients of such equations when little theoretical evidence is available. However, other relationships have been derived from first principles with certain assumptions concerning molecular motions.

Bueche (135, 172) considered both dilute solutions and bulk polymers. During shear, a spherical free draining molecule is alternately compressed and stretched whilst rotating in the direction of the applied force. A similar mathematical approach was derived by Debye (134).

Ree and Eyring (173) considered flow in terms of a number of different flow species within the fluid per unit area of the shear plane, each contributing to the stress. The shear stress was then the summation over all flow species.

The Doi-Edwards theory (174-177) uses a different approach to shear thinning in entangled systems. The model assumes that a molecule is contained within a tube of the same length. Entanglement effects become significant when the shear rate is less than the reciprocal time taken for the entire molecule to diffuse out of the tube. Hence, disentanglement takes place faster than entanglement and good qualitative agreement with experimental data was achieved.

Although some of the above mentioned theories have been available for a long time, their application to experimental data is far from universal. This is because the theories are derived for single polymers with narrow molecular weight

distributions in solutions without other substances present. In contrast, systems of pharmaceutical interest always contain several ingredients and the non-Newtonian behaviour may only be quantified using semi-empirical or wholly empirical equations. A few of these equations were listed in Table 2.3.. The ubiquity of such empirical equations is the result of of rheological measurements on numerous different materials by many different methods. In this study, the 'Structure Equation' due to Shangraw et al (97) was found to adequately model all the continuous shear experimental data.

The relationship is based on the hypothesis of Williamson (178) that the shear stress, τ, measured during a continuous shear test of a pseudoplastic sample is made up of two component stresses τ_1, and τ_2. In common with Williamson, Shangraw used the equation for plastic flow to describe τ_1, ie:

$$\tau_1 = f + \eta_\infty \dot{\gamma} \qquad\qquad 3.1.$$

where f = yield stress

η_∞ = viscosity coefficient

$\dot{\gamma}$ = shear rate

Whilst Williamson considered τ_2 to be a hyperbolic function of $\dot{\gamma}$, Shangraw chose an exponential form such that

$$\tau_2 = b_V \exp^{-a\dot{\gamma}} \qquad\qquad 3.2.$$

where b_V = coefficient of viscous resistance

a = constant with the units of time

Since the exponential term represents shear thinning, the component stresses are combined as $\tau = \tau_1 - \tau_2$. Therefore

$$\tau = f + \eta_\infty \dot{\gamma} - b_V \exp^{-a\dot{\gamma}} . \qquad\qquad 3.3.$$

which is the Shangraw 'Structure' Equation. When $\dot{\gamma} = 0$,

$\tau = f - b_v$ which is claimed to represent the yield stress.

This conflicts with Equation 3.1. where f alone is the yield

stress. Therefore little weight can be placed on the physical

significance of these coefficients, although η_∞ agrees well

with the high shear limiting viscosity.

3.3 Materials and Methods

The Sodium Alginate used was Protonal LFR5/60 as in Section 2;

the 'Carbopol' was of pharmaceutical grade 934P [1]; the Xanthan

gum was 'Keltrol F' [2] and Thiomersal was of laboratory reagent

grade [3].

3.3.1 Rheological Testing

The experimental technique of oscillatory testing has been

detailed in Section 2.3.4.2. To test for linear

viscoelasticity in a narrow range, representative samples were

tested for input amplitudes of 1.7 and 4.3 x 10^{-3} rad. No

significant differences in amplitude ratio, ν , or phase lag, C ,

were found, therefore all samples were tested using the minimum

amplitude necessary.

Repeated testing of several viscoelastic samples showed that

G' and η' could be determined with a precision of $\pm$ 5%.

However, at low phase angles, small errors in C lead to large

errors in η' due to the Sin term in Equation 2.24.: at values

of ν approaching 1.0., small errors in ν lead to large errors

in G'. Both of these aspects are quantified in Figure 3.3.

[1] B.F.Goodrich, Cleveland, Ohio, USA.
[2] Kelco Co., San Diego, California, USA.
[3] B.D.H., Poole, Dorset, UK.

Figure 3.3. Precision of Storage Modulus, G',
and Dynamic Viscosity, η', Values at High
Amplitude Ratio ν and Low Phase Angle C
Respectively. Amplitude Ratio (broken line) :
Error in G' (ω) determined from a precision of
±0.002; C = 0 rad, ω = 0.792 rad s^{-1}. Phase
Angle (solid line) : Error in η' (ω) determined
from a precision of ±0.0087 rad; ν = 0.5,
ω = 0.792 rad s^{-1}).
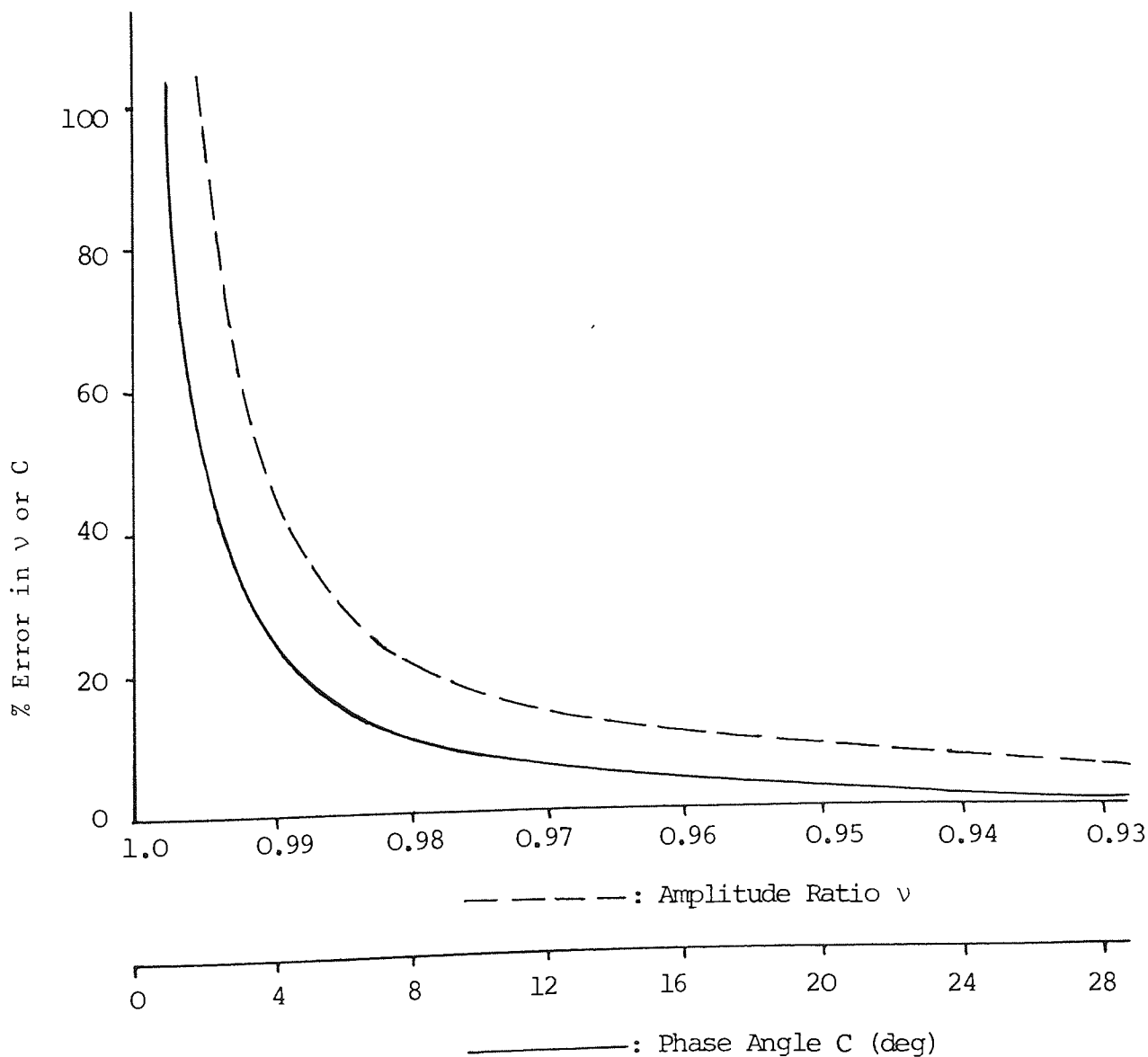
showing that additional significant errors are introduced at

$C \neq 0$, $C \gtrsim 15^0$ and $\nu < 0.96$.

Continuous shear testing was carried out using a Rheomat 30 viscometer [1], the basic design of which is shown in Figure 3.4. A variable speed motor rotating at known angular velocity, applies a shear rate <u>via</u> the upper member of the system and the resultant torque on the sample is monitored. By calibration, a $\tau(\dot{\gamma})$ rheogram curve was constructed automatically with an X-Y chart recorder [2].

In order to maintain certain consistencies with the rheogoniometer, cone and plate geometry was used. The non-truncated cone angle was $30'54''$ and the plate diameter 5.312 cm. Tests were carried out at 21.5^0 C with applied shear rates starting at 53.6 $\sec^{-1}$ and taking 0.5 min to reach the peak of 3950 $\sec^{-1}$. Only up-curves were analysed although down-curves were also obtained. Attempts were made to fit the data to several empirical equations using graphical analysis and non-linear regression analysis routine, 'NONLIN' (179).
From these, Equation 3.3., derived by Shangraw, was used throughout. Similar regression analysis using the 'Structure' Equation 3.3. was recommended by Neibergall <u>et</u> <u>al</u> (180).

[1] Contraves AG, Schaffhauserstrasse 580, CH-8052, Zurich,
                                        Switzerland.

[2] Bryans Model 25000, Bryans Southern Instruments Limited,
                                        Mitcham, Surrey, UK.

Figure 3.4.   BASIC PRINCIPLES OF THE 'RHEOMAT 30' VISCOMETER.
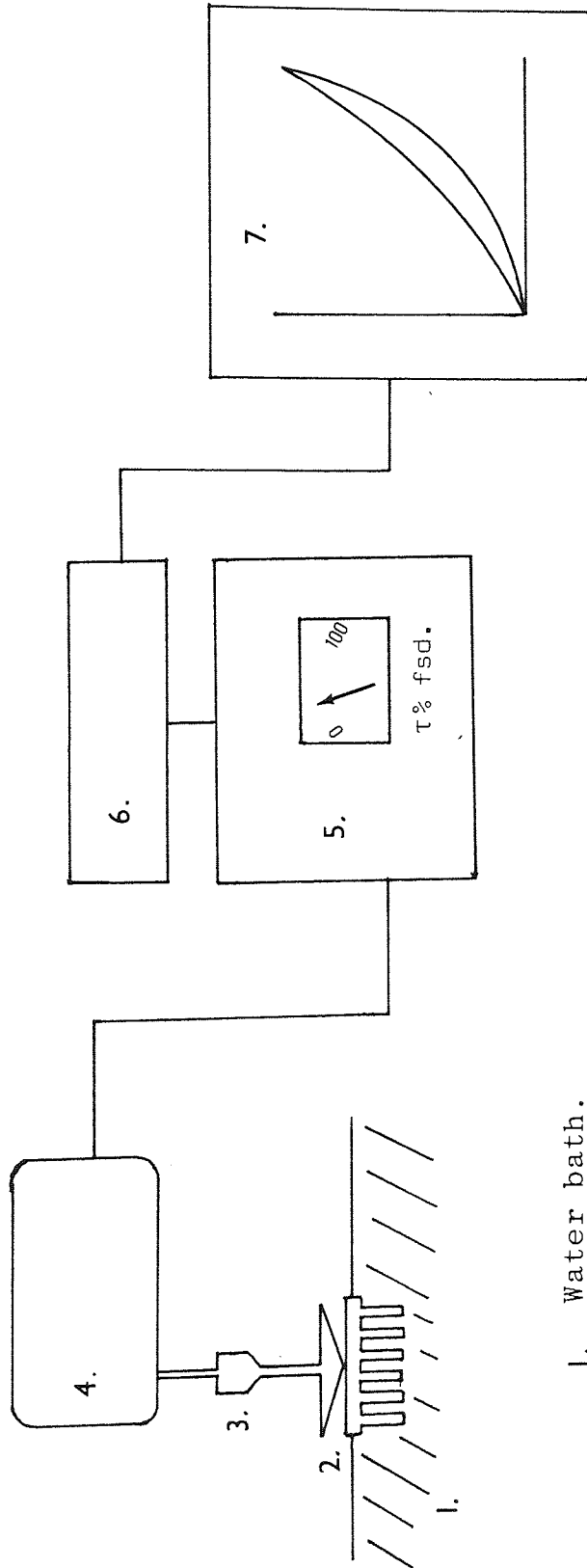
1.   Water bath.

2.   Cone and Plate geometry.

3.   Rotating shaft.

4.   Motor and torque sensor by torsion bar.

5.   Amplifier for torque and tachometer signals.

6.   Automatic shear rate programmer.

7.   X-Y chart recorder.

3.3.2 Preparation of Samples

Samples of mixtures of suspending agents were prepared by using two separate methods.

Method A - Industrial Pilot Plant Equipment.

Dispersions or solutions of Carbopol, Xanthan gum or Sodium Alginate in deionised water were obtained using a 'Lightnin'[1] high speed mixer with a 10 cm blade paddle stirrer. Thiomersal 0.002% w/w was included as a preservative. Carbopol was neutralised to pH 7 using 20% w/w NaOH, and suspending agents combined in a 5 Kg capacity 'Hobart'[2] planetary mixer. When the effect of additional high shear was investigated, a 'Silverson' AXR homogeniser[3] was employed. It was used at the maximum speed setting and contained the small square mesh which produced high shearing of the sample.

Method B - Laboratory Scale Equipment.

The minimum necessary shear required for dispersion was achieved using a Heidolph variable speed stirrer motor[4] with a 3 cm stainless steel paddle blade. Admixtures were prepared manually by stirring in a glass beaker.

Samples prepared by each method were centrifuged to remove air bubbles and for comparison of methods A and B, samples were stored at 20^0C for at least seven days prior to rheological measurement.

[1] Lightnin Mixers Ltd., Stockport, Cheshire, U.K.
[2] Hobart Manuf. Co. Ltd., New Southgate, London, N11, U.K.
[3] Silverson Machines Ltd., Waterside, Chesham, Bucks. U.K.
[4] Heidolph Elektro KG, W.Germany

3.3.3 Sedimentation Tests

When Xanthan gum and Sodium Alginate solutions were mixed
without shearing, sedimentation of the denser Xanthan phase
occurred. The sedimentation heights were determined in
10×2 cm specimen tubes stored at $20\,^0C$ for five months and
compared with samples that had been sheared using the
'Silverson' homogeniser.

3.4 Results

The rheological data obtained from oscillatory testing is
presented as $G'(\omega)$ and $\eta'(\omega)$, ie, the real components of the
complex modulus and viscosity respectively. The appearance of
plateaux indicates limiting elastic or viscous behaviour at
high and low frequencies respectively; besides this, the
manner in which either G' or η' change with ω is characteristic
of the system.

Within Sections 3.4.1. and 3.4.2., all $G'(\omega)$ and $\eta'(\omega)$ curves
are drawn to the same scale for comparison purposes, although
the ordinate may be shifted vertically.

3.4.1 Xanthan Gum Systems

3.4.1.1 Effect of Concentration

As would be expected, G' and η' both increased with Xanthan
concentration as shown in Figures 3.5., 3.6. and summarised
for $\omega = 25$ rad s^{-1} in Figure 3.7 (a) and (b). $G'(\omega)$ shows
curvature with a tendency to plateau at perhaps 10^2 to 10^3
rad s^{-1} ; for $\eta'(\omega)$, no clue is apparent as to the lower

Figure 3.5. The Effect of the Frequency of Oscillation on the Storage Modulus of Various Concentrations of Xanthan Gum Solutions.

Concentrations (% w/w) : 0.4 ▽ ,0.5 △ ,0.7 ▲ ,0.8 ▲ ,1.0 ○ , 1.5 ◑ ,1.8 ◐ ,4.0 ● .
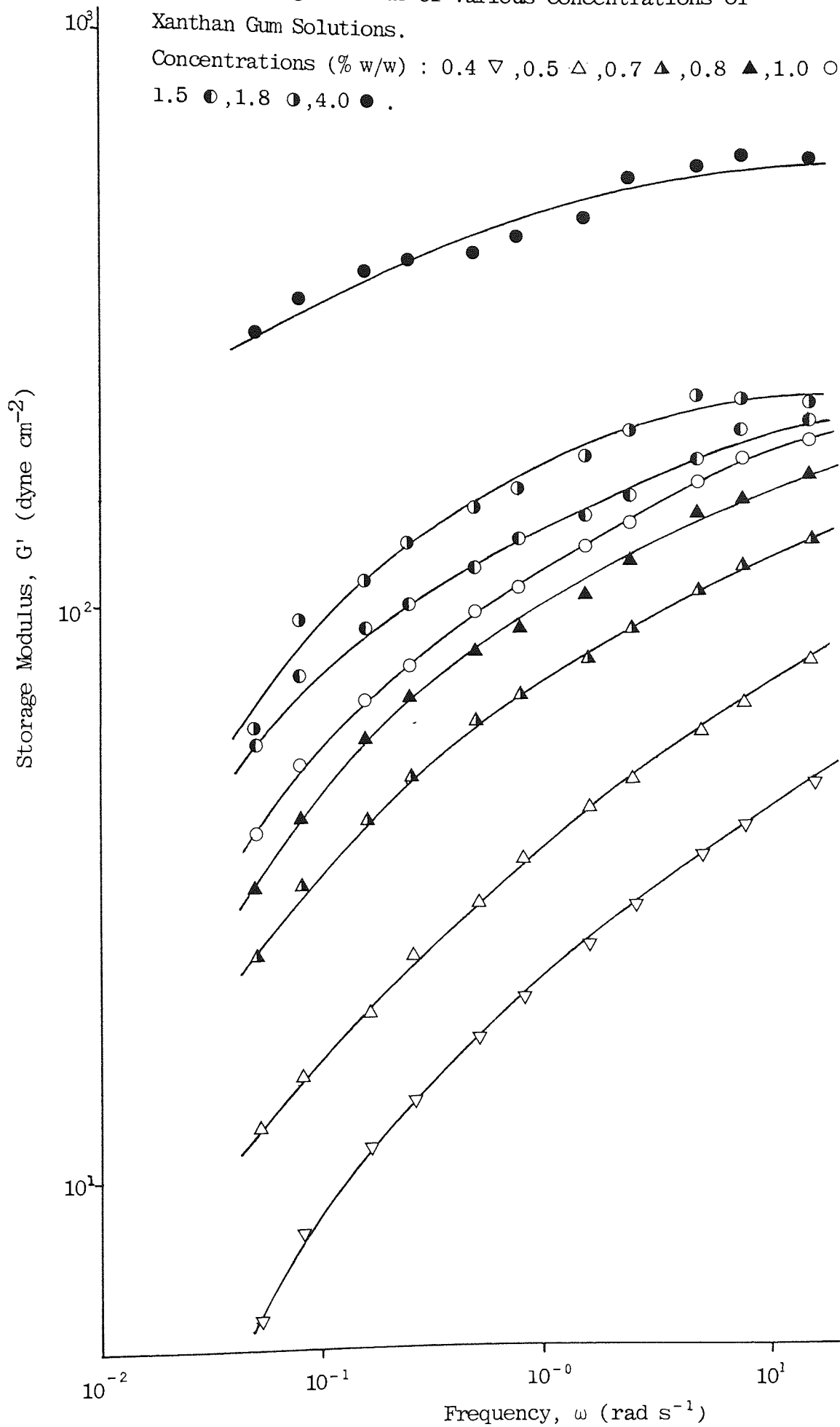
Figure 3.6. The Effect of the Frequency of Oscillation on the Dynamic Viscosity of Various Concentrations of Xanthan Gum Solution.

Concentrations (% w/w) : 0.4 ▽ ,0.5 △ ,0.7 ▲ ,0.8 ▲ ,1.8 ◑, 4.0 ●.
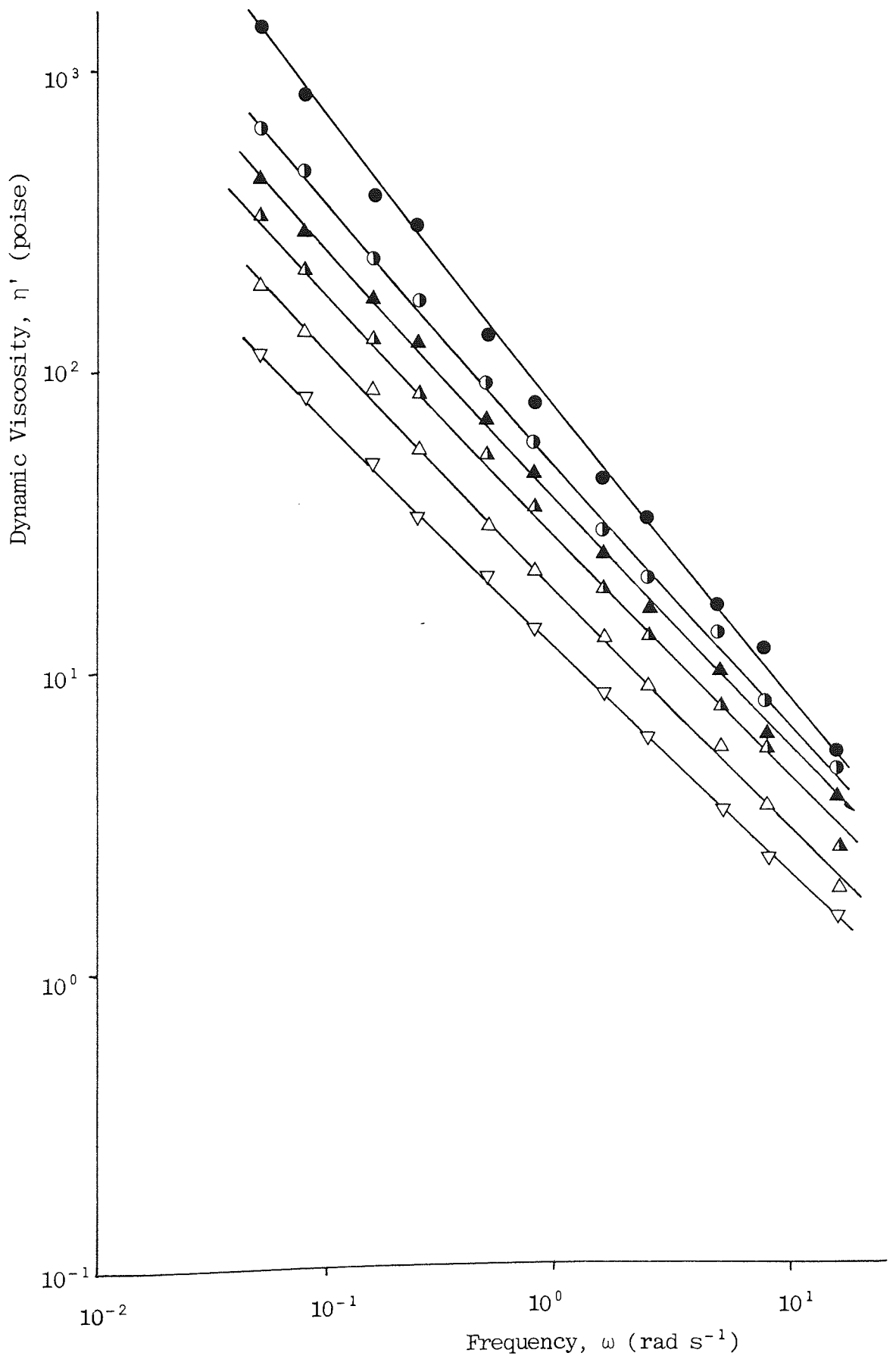
Figure 3.7. The Effect of the Concentration of Xanthan Gum in Solution on the Viscoelastic Parameters at Oscillation Frequency $\omega = 2.5$ rad s^{-1}.

(a) Storage Modulus, G' ●   (b) Dynamic Viscosity, η' ◑
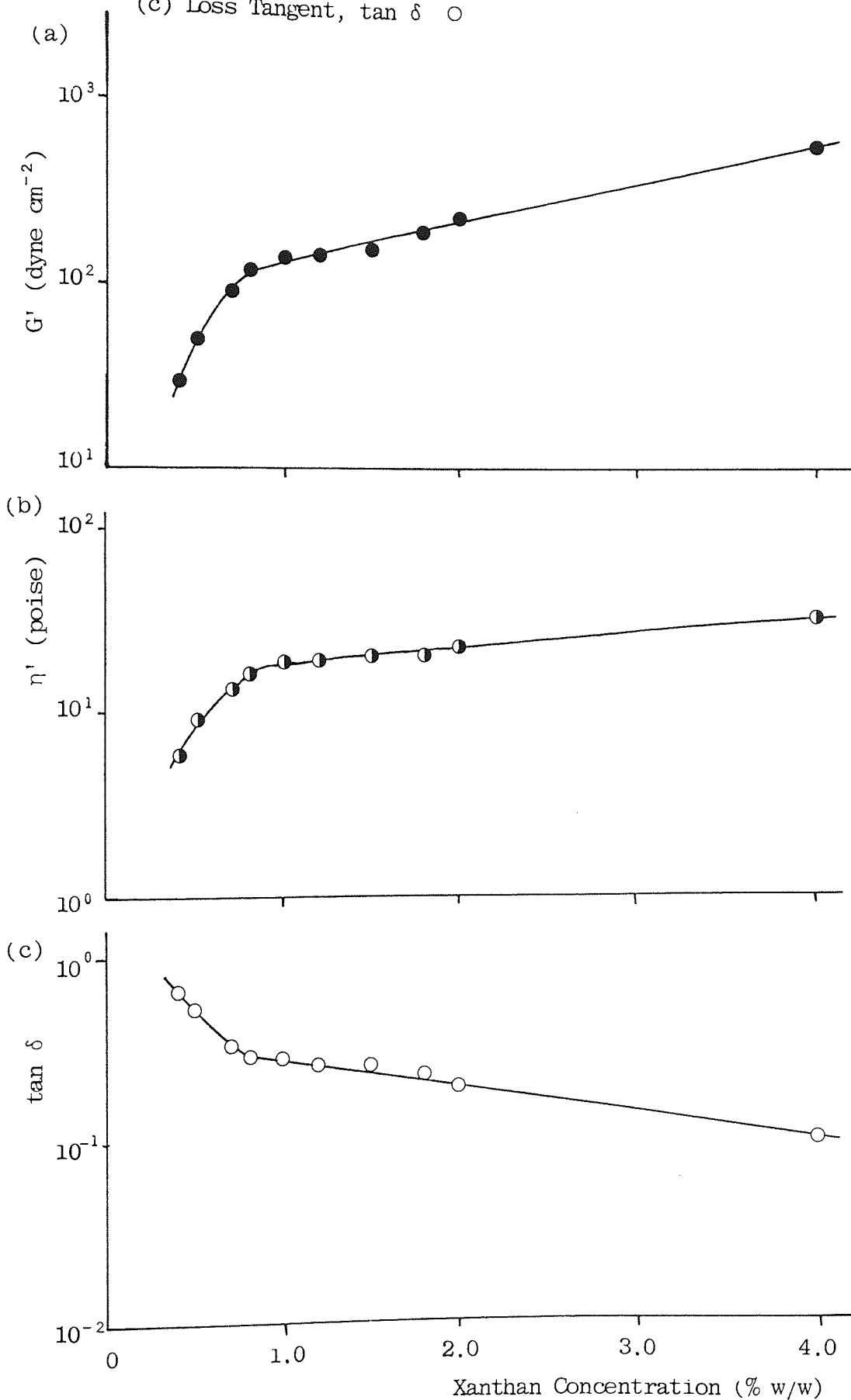
(c) Loss Tangent, tan δ ○

frequency necessary to attain a limiting viscosity η_0.

The loss tangent, tan δ (ω) curves in Figure 3.8., which are summarised for $\omega = 2.5$ rad s^{-1} in Figure 3.7.(c), tell us that although both elastic (storage) and viscous (loss) components increased with concentration, the former increased more rapidly. Hence, one would expect the higher Xanthan concentrations to exhibit gel-like rigidity, which did in fact occur.

With regard to the mixed Xanthan and Alginate systems, there was an interesting contrast. Increasing the concentration of Xanthan in Alginate solutions showed a different effect to increasing the concentration of Alginate in Xanthan solutions. In the case of the former, see Figure 3.9. to 3.13., the viscoelastic parameters increased steadily but in the latter instance, see Figures 3.14 to 3.16., the concentration range 1.0 to 3.0 % w/w Alginate had a very marked effect. In this range, G' (ω) and η' (ω) were reduced by a logarithmic cycle whereas other concentrations had relatively little effect. This infers that the Alginate was being 'titrated' against the Xanthan and that the concentration range 1.0 to 3.0% w/w Alginate represents the end-point.

3.4.1.2 Effect of Preparation Method

The high speed mixer used in the industrial 'pilot scale' preparation, Method A, was found to cause irreversible shear breakdown of the Xanthan-Alginate mixes studied. With

Figure 3.8. The Effect of the Frequency of Oscillation on the Loss Tangent of Various Concentrations of Xanthan Gum Solution.

Concentrations (% w/w) : 0.4 ▽ ,1.0 ○ ,2.0 ▼ ,4.0 ● .

Figure 3.9. The Effect of the Concentration of Xanthan Gum in Sodium Alginate 5% w/w Solution on the Storage Modulus, G' plotted as a function of the Frequency of Oscillation. Method A. Industrial Pilot Scale Preparation.

Concentrations (% w/w) : 0.5 △ ,0.8 ○ ,1.0 ◐ ,1.3 ◑ ,2.0 ● .

Figure 3.10. The Effect of Concentration of
Xanthan Gum in Sodium Alginate 5% w/w Solution
on the Storage Modulus, G', plotted as a
function of the Frequency of Oscillation, ω.

Method B : Laboratory Scale Preparation.

Xanthan Concentrations (% w/w) : 0.2 △, 0.4 ○,

0.5 ◑, 0.8 ◕, 1.0 ●.
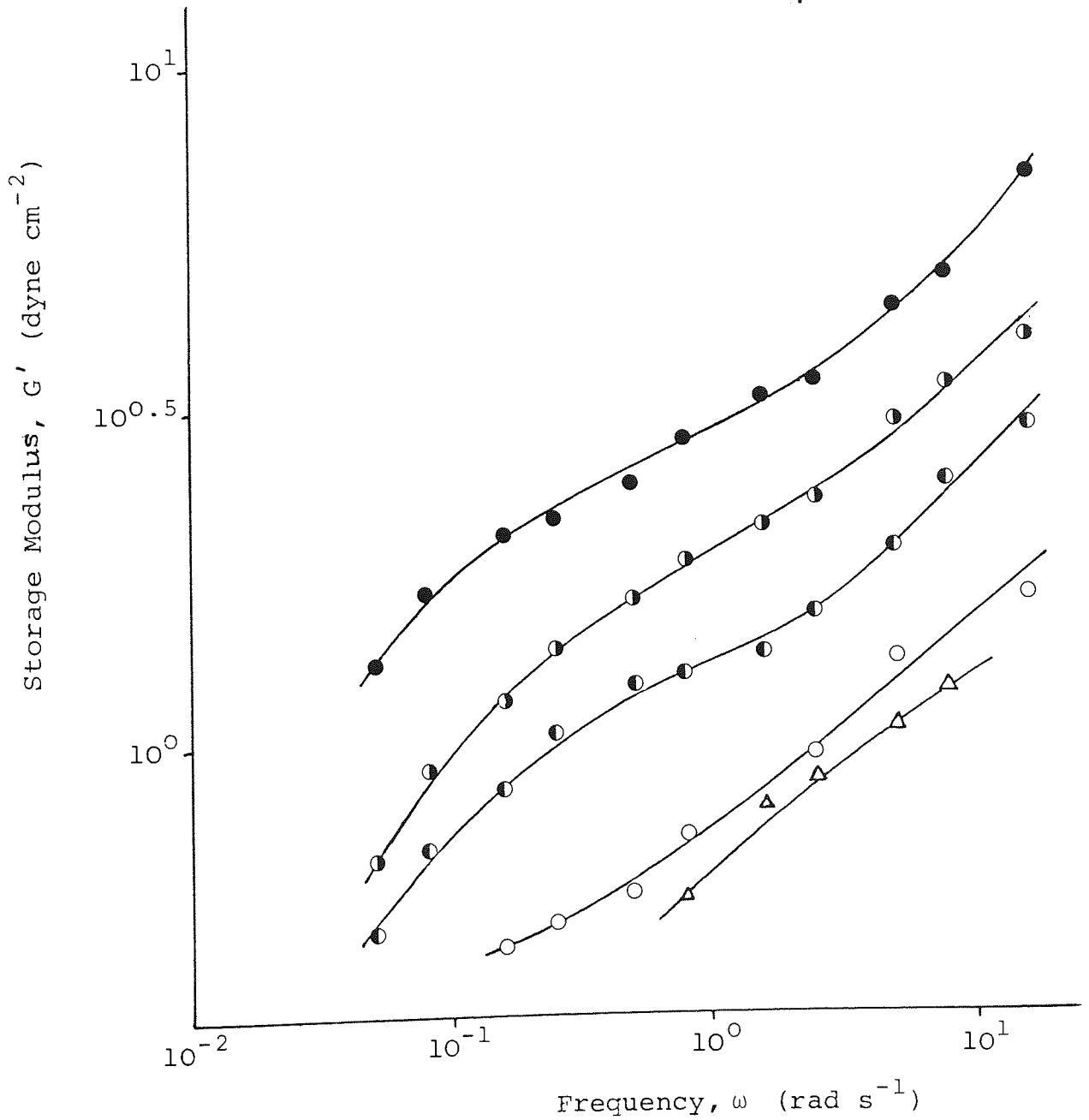
Figure 3.11. The Effect of Concentration of Xanthan Gum in Sodium Alginate 5% w/w Solution on the Dynamic Viscosity, η', plotted as a function of the Frequency of Oscillation, ω .

Method A : Industrial Pilot Scale Preparation.
Xanthan Concentrations (% w/w) : 0.0 △, 0.5 ○, 0.8 ◑,
1.3 ◐, 2.0 ●.
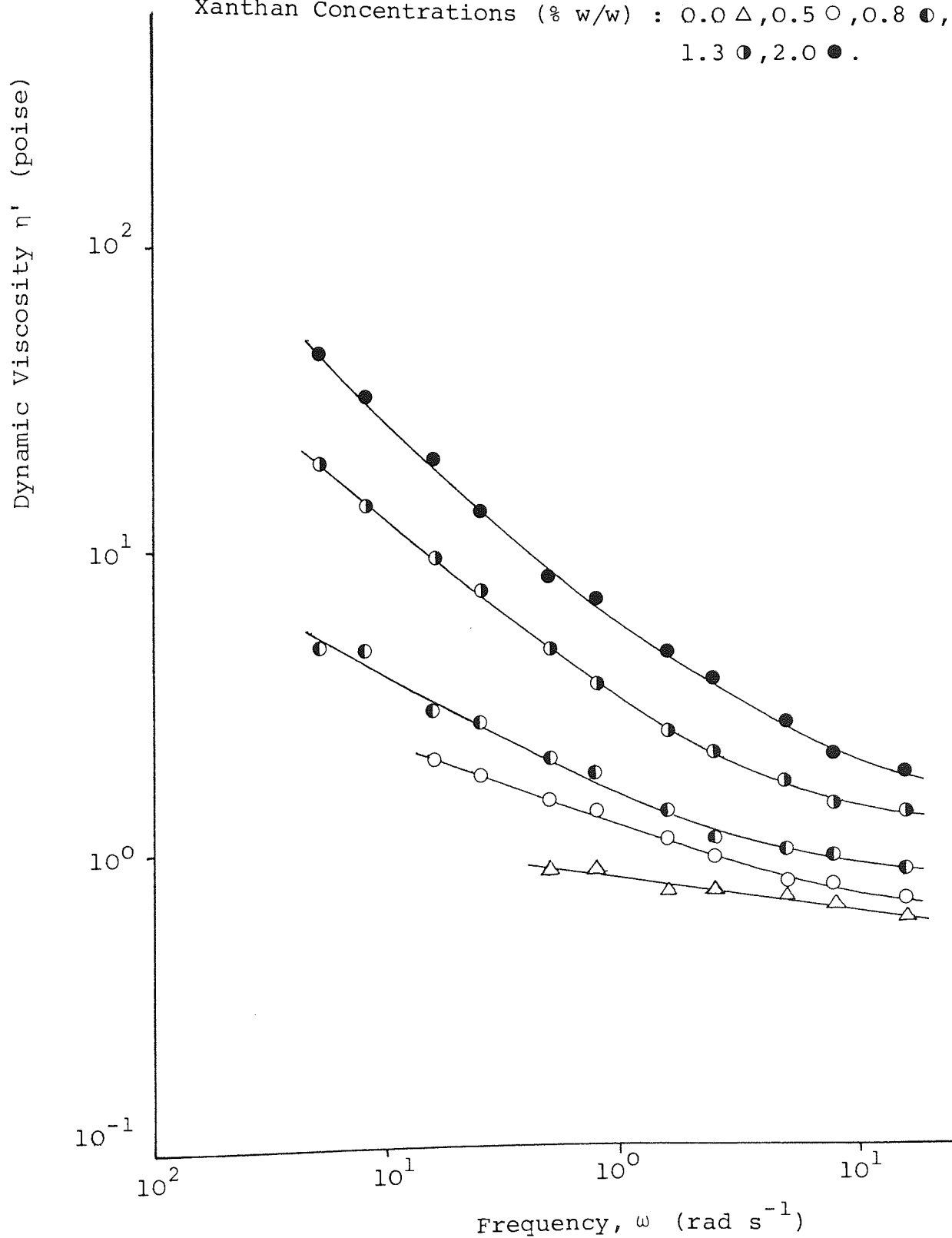
Figure 3.12. The Effect of Concentration of Xanthan Gum in Sodium Alginate 5% w/w Solution on the Dynamic Viscosity, η', plotted as a function of the Frequency of Oscillation, ω.

Method B : Laboratory Scale Preparation.

Xanthan Concentrations (% w/w) : 0.2 △, 0.4 ○, 0.5 ◐,

0.8 ◑, 1.0 ●

Figure 3.13. The Effect of Concentration of Xanthan Gum in Sodium Alginate 5% w/w Solution on (a) Dynamic Viscosity and (b) Storage Modulus at Oscillation Frequency, $\omega = 2.5$ rad s^{-1}. Method A, Industrial Scale Preparation Before Shearing ◐ Method A, Industrial Scale Preparation After Shearing ○ Method B, Laboratory Scale Preparation, ●.

(a)

(b)

Xanthan concentration C (g 100g^{-1})

Figure 3.14. The Effect of the Concentration of
Sodium Alginate in Xanthan Gum 2% w/w Solution
on the Storage Modulus G', plotted as a function
of the Frequency of Oscillation, ω.

Concentrations (% w/w) : 0.0 ●,0.5 ◐,1.0 ◑,2.0 ◒
2.5 ▲,3.0 △,4.0 ▽,5.0 ▼
8.0 △.

Figure 3.14 (see facing page)

Figure 3.15. The Effect of the Concentration of Sodium Alginate in Xanthan Gum 2% w/w Solution on the Dynamic Viscosity, η', plotted as a function of the Frequency of Oscillation, ω.

Alginate Concentrations (% w/w) : 0.0 ●,2.5 ▲,3.0 ▲,8.0 △.
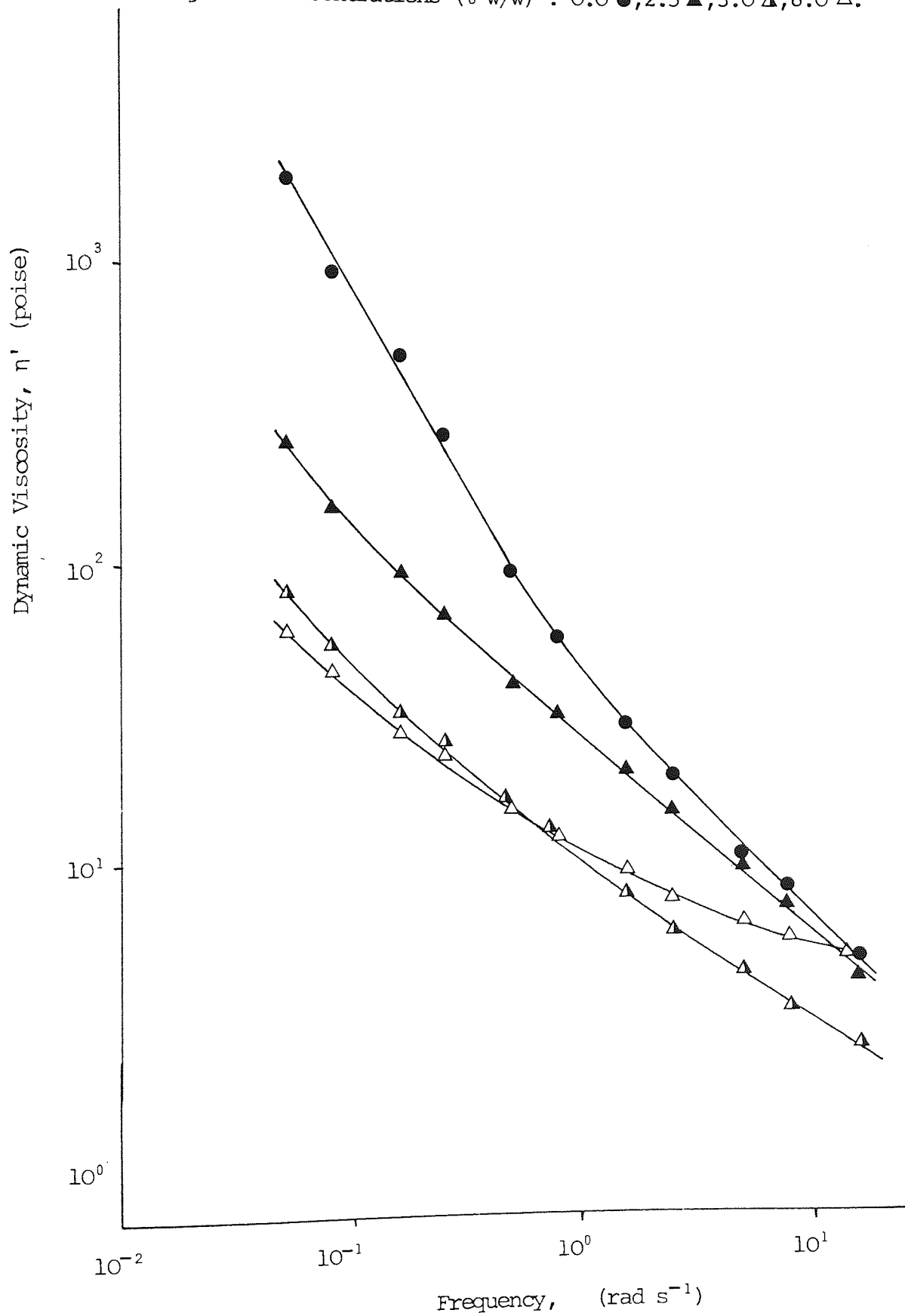
Figure 3.16. The Effect of Concentration of Sodium Alginate in Xanthan Gum 2% ^{w}/w Solution on (a) Dynamic Viscosity and (b) Storage Modulus at Oscillation Frequency $\omega = 2.5$ rad s^{-1}, and the Effect of High Shear. Before High Shear, ● ; After High Shear ○ .
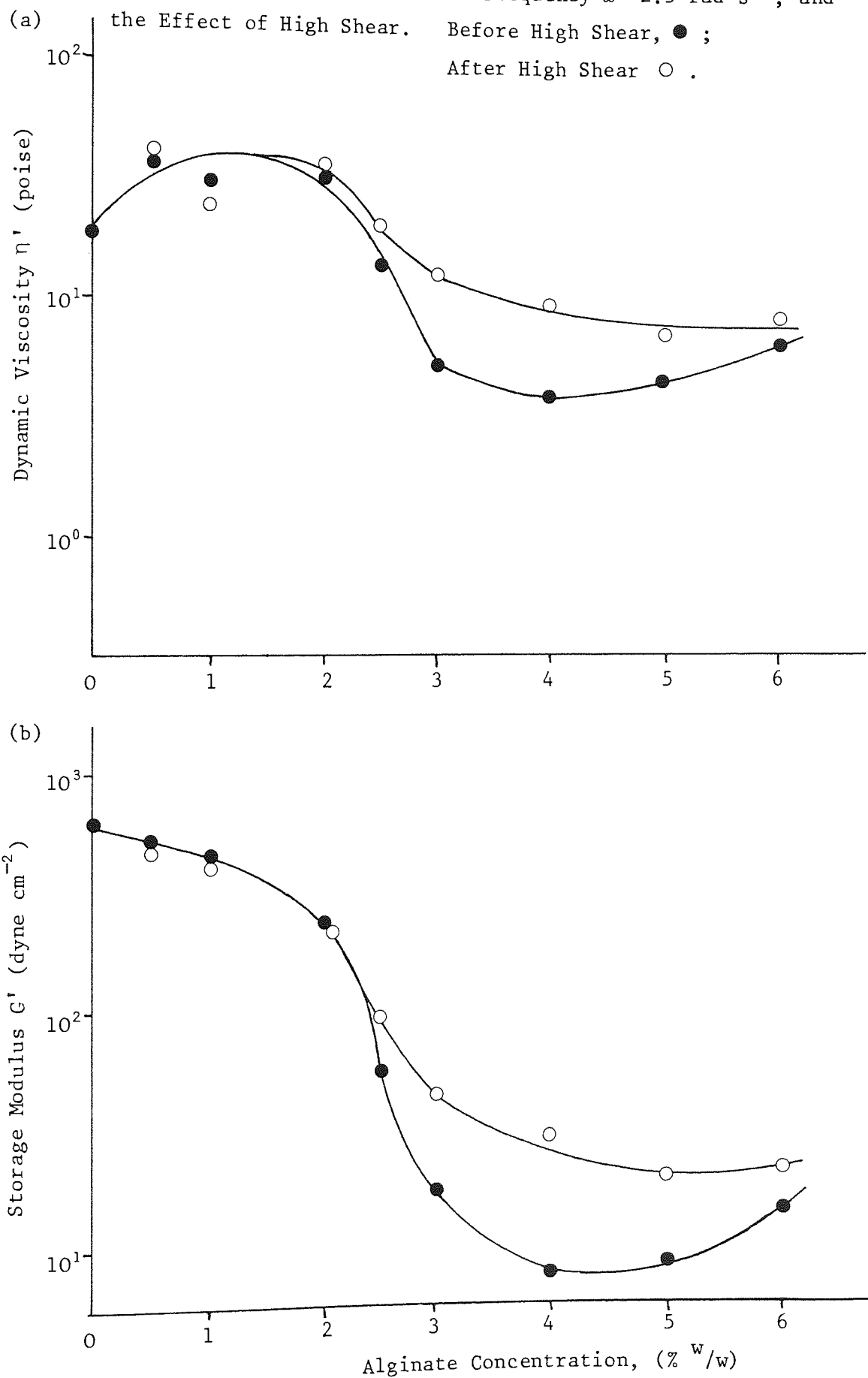
reference to Figures 3.9 to 3.12., G' (ω) and η' (ω) were significantly higher for the relatively low shear samples prepared by Method B. Figures 3.13. (a) and (b), which summarise G' and η' at $\omega = 2.5$ rad s^{-1} as a function of Xanthan concentration, show that the effect was marked for elasticity. The intrinsic modulus, $[G'_\omega]_{c=0}$ obtained by extrapolation of Figure 3.13. (b) to zero Xanthan concentration, is 0.52 dyne cm^{-2} for Method B but only 0.20 dyne cm^{-2} for Method A. This suggests that the effect of the mixing time in an industrial situation can be quantitatively linked with the rheological performance of the final product. For example, if the suspending ability of the vehicle is correlated with η_0, (137), then the mixing time may not be so critical with respect to the physical stability as if the instantaneous modulus G_0, (138), had been correlated.

Twelve Xanthan – Alginate mixes were prepared on two separate occasions using Method A. The samples were allowed to equilibrate for similar periods of time prior to rheological testing. The viscoelastic parameters measured using the Weissenberg Rheogoniometer occasionally differed by more than 5% but the distribution of differences was non-systematic.

Comparison of the two preparation methods show the results to be consistent with a significant irreversible shear breakdown of the Xanthan gum leading to reduced gel-like properties of the Xanthan-Alginate mixes. The Sodium Alginate used was of low molecular weight and prolonged shearing of a 10% w/w

solution did not reduce the viscoelastic parameters
significantly below those found in Section 2.4.4.

3.4.1.3 Effect of Shearing

It was found that low shear blending in a planetary mixer did
not produce stable Xanthan-Alginate mixes; separation of the
denser Xanthan phase occurred unless good blending was achieved
by applying high shear for example, by the use of a 'Silverson'
mixer. The effect of high shear on the separation of Xanthan
was quantified by monitoring the sedimentation rate of the
Xanthan component. Rate constants were obtained from
first order plots of the sedimentation ratio against time.

Figure 3.17. shows that increasing the concentration of Xanthan
in Alginate solution reduced the separation rates as would be
expected; increasing the Alginate content in Xanthan solution
did not yield a significant trend. The sedimentation rate
data before and after shearing is given in Table 3.1.. More
importantly, after shearing the samples for 5 min. using the
'Silverson' mixer, the separation rates were extremely low.

To study the effect of shearing time and subsequent recovery
on rheological properties, Xanthan 2% – Alginate 5% w/w mix
was sheared for 0,5,10,20,40, min. and oscillatory shear
measurements were made 24 hours after preparation. The
results given in Figures 3.18. and 3.19. for G' (ω) and η' (ω)
respectively, show than on shearing, the elastic component was
increased by a greater proportion than the viscous component.

Figure 3.17. The Effect of the Concentration of Xanthan Gum in Alginate 5% w/w Solution on the First Order Rate Constant for the Decreasing Sedimentation Ratio.
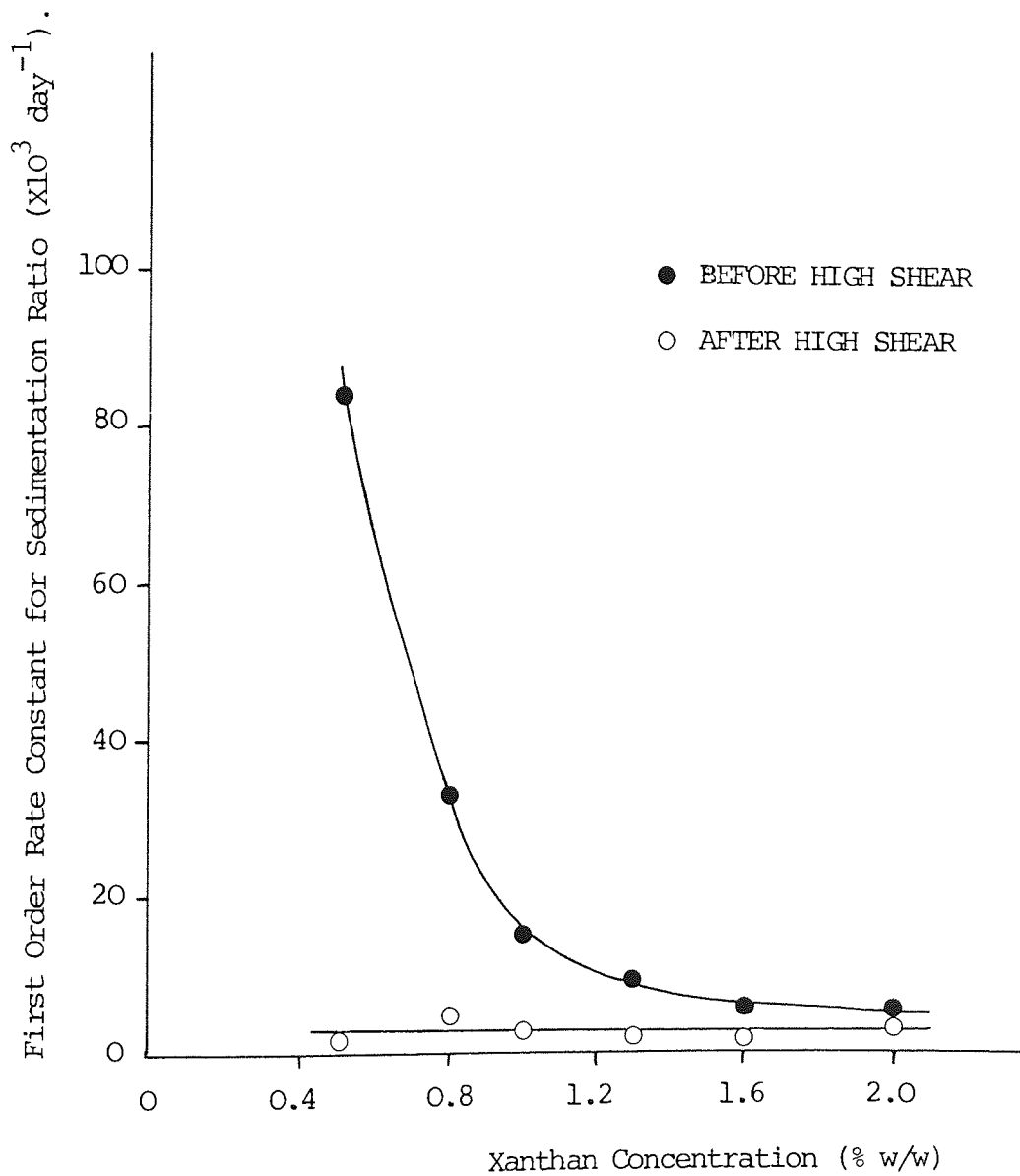
Table 3.1   The Effect of Storage Time at 20°C on the Sedimentation
Ratios of Xanthan Gum Solution in Sodium Alginate 5% w/w
Solution: (a) before and (b) after shearing.

(a) Before Shearing

Time (days)	Sedimentation Ratio, F					
	Xanthan Gum Concentration (% w/w)					
	0.5	0.8	1.0	1.3	1.6	2.0
3.75	0.767	0.901	0.949	0.949	0.976	0.966
4.75	0.706	0.870	0.942	0.942	0.970	0.953
6.9	0.558	0.815	0.917	0.923	0.959	0.953
7.9	0.509	0.790	0.904	0.910	0.959	0.946
12	0.344	0.679	0.846	0.878	0.935	0.913
15	0.270	0.605	0.801	0.833	0.917	0.903
19	0.221	0.506	0.750	0.801	0.888	0.859
26	0.208	0.415	0.672	0.755	0.842	0.800
34	0.190	0.302	0.596	0.708	0.805	0.767
39	0.184	0.278	0.551	0.672	0.781	0.734
50	0.184	0.196	0.474	0.604	0.722	0.624
76	0.178	0.195	0.404	0.553	0.604	0.570
88	0.172	0.195	0.378	0.521	0.550	0.570
95	0.166	0.190	0.378	0.514	0.538	0.557
144	0.160	0.190	0.340	0.582	0.542	0.523
r *	-0.9935	-0.9981	-0.9995	-0.9982	-0.9989	-0.9952
K *	-0.0847	-0.0377	-0.0154	-0.00978	-0.00657	-0.00610
i *	0.016	0.0097	0.0123	0.020	0.0055	0.012

*   Correlation coefficient, r, slope K (day^{-1}), and intercept, i,
of first order plots of Ln (F) against time.

Table 3.1. The Effect of Storage Time at 20°C on the Sedimen-tation Ratios of Xanthan Gum Solution in Sodium Alginate 5% w/w Solution: (a) before and (b) after shearing.

(b) After Shearing.

Time (days)	Sedimentation Ratio, F					
	Xanthan Gum Concentration (% w/w)					
	0.5	0.8	1.0	1.3	1.6	2.0
3.75	0.994	1.0	1.0	1.0	1.0	0.988
4.75	1.0	1.0	1.0	1.0	1.0	0.988
6.9	0.994	1.0	1.0	1.0	1.0	0.963
7.9	0.988	1.0	1.0	1.0	1.0	0.963
12	0.969	0.987	1.0	0.994	1.0	0.951
15	0.957	0.967	0.975	0.969	1.0	0.921
19	0.957	0.960	0.969	0.963	0.965	0.915
26	0.942	0.921	0.943	0.939	0.958	0.889
34	0.920	0.880	0.938	0.920	0.943	0.854
39	0.914	0.860	0.925	0.907	0.943	0.841
50	0.889	0.813	0.901	0.889	0.922	0.805
76	0.858	0.720	0.870	0.846	0.887	0.774
88	0.827	0.673	0.839	0.809	0.851	0.774
95	0.815	0.660	0.826	0.809	0.851	0.738
144	0.747	0.567	0.770	0.753	0.830	0.713
r *	−0.9941	−0.9993	−0.9965	−0.9867	−0.9908	−0.9948
K *	−0.0021	−0.0049	−0.0020	−0.0021	−0.0017	−0.0044
i *	−0.0035	0.044	0.043	0.0043	0.0428	0.0016

* Correlation coefficient, r, slope K (day^{-1}), and intercept, i, of first order plots of Ln (F) against time.

Figure 3.18. The Effect of the Shearing Time on the Storage
Modulus G', of a Solution containing Xanthan Gum 2% w/w and
Sodium Alginate 5% w/w, plotted as a function of the Frequency
of Oscillation, ω .

Shearing Times (min.): 0 △,5 ○,10 ○,20 ○,40 ●.

Storage Modulus, G' (dyne cm^{-2}).

Frequency, ω (rad s^{-1}).
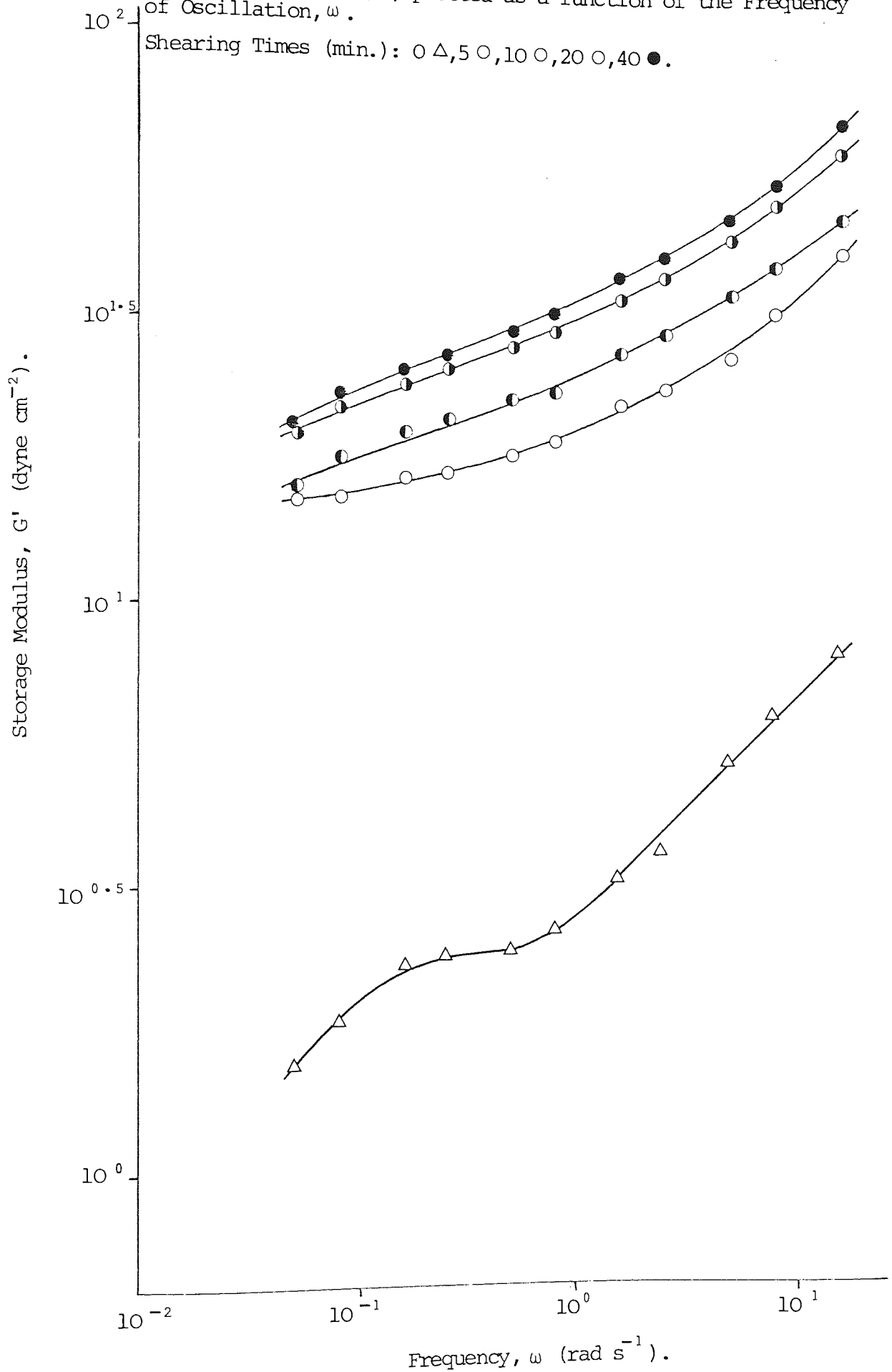
Figure 3.19. The Effect of the Shearing Time on the Dynamic Viscosity, η', of a Solution containing Sodium Alginate 5% w/w, plotted as a function of the Frequency of Oscillation, ω.

Shearing Times (min) : 0 △, 5 ○, 10 ◑, 20 ◐, 40 ●.
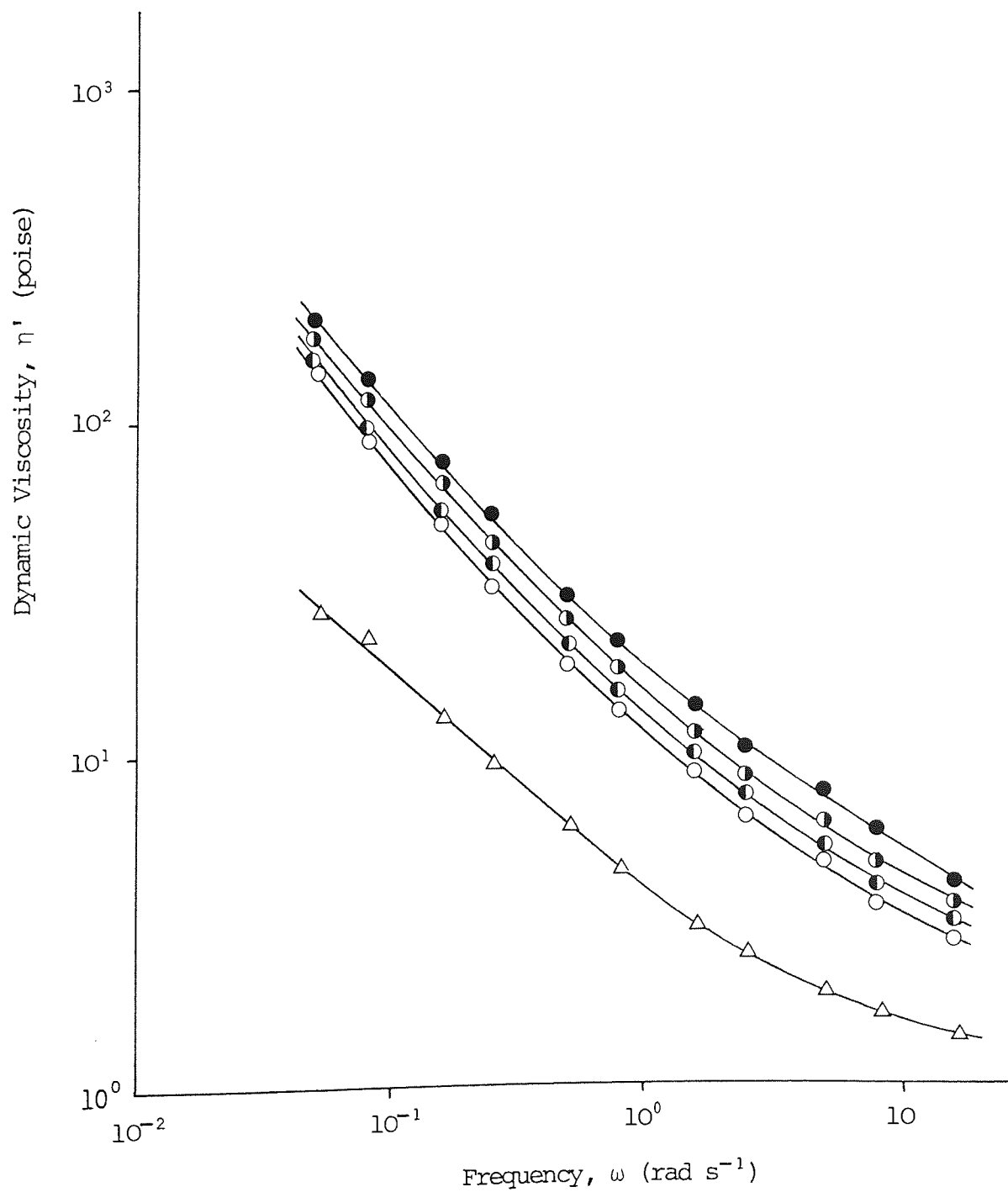
That the increases applied to absolute values is illustrated in Figure 3.20. where the percentage increase in G' at $\omega = 1.57$ rad s^{-1} is significantly greater than that for η' (P > 0.995). This tends to support the similar findings of Section 3.4.1.2.

Measurements made at time intervals from 24 to 264 hours after preparation showed no significant increase in the viscoelastic parameters which indicated that the structural recovery was either longer or shorter than the time period studied. Shearing of 0.6 and 2.0% w/w Xanthan solutions using the 'Silverson' mixer had no significant effect on G' (ω) or η' (ω) when measured up to 264 hours after preparation.

3.4.2 'Carbopol' Systems

3.4.2.1 Effect of Concentration

Carbopol alone in neutralised solution exhibits completely different rheological characteristics to Xanthan Gum, but certain similarities appear on admixture with Alginate. Figure 3.21. of G' (ω) for Carbopol above shows the result that solutions were almost purely elastic when the concentration was less than 0.5% w/w concentration. The summarised data in Figure 3.22. for G' at $\omega = 2.5$ rad s^{-1} suggests that increasing the concentration above 1.0% w/w does not significantly increase the storage modulus. It is probably more accurate to say that the increase in G' at high concentrations lies within the limits of error inherent when ν approaches 1.0 as shown in

Figure 3.20. Percentage Increases in Storage Modulus, ● ,
and Dynamic Viscosity, ○ , at $\omega = 1.57$ rad s^{-1} as a
function of the Shearing Time of a Xanthan 2%, Alginate
5% w/w mix.

Error bars show 95% confidence limits (n = 5).
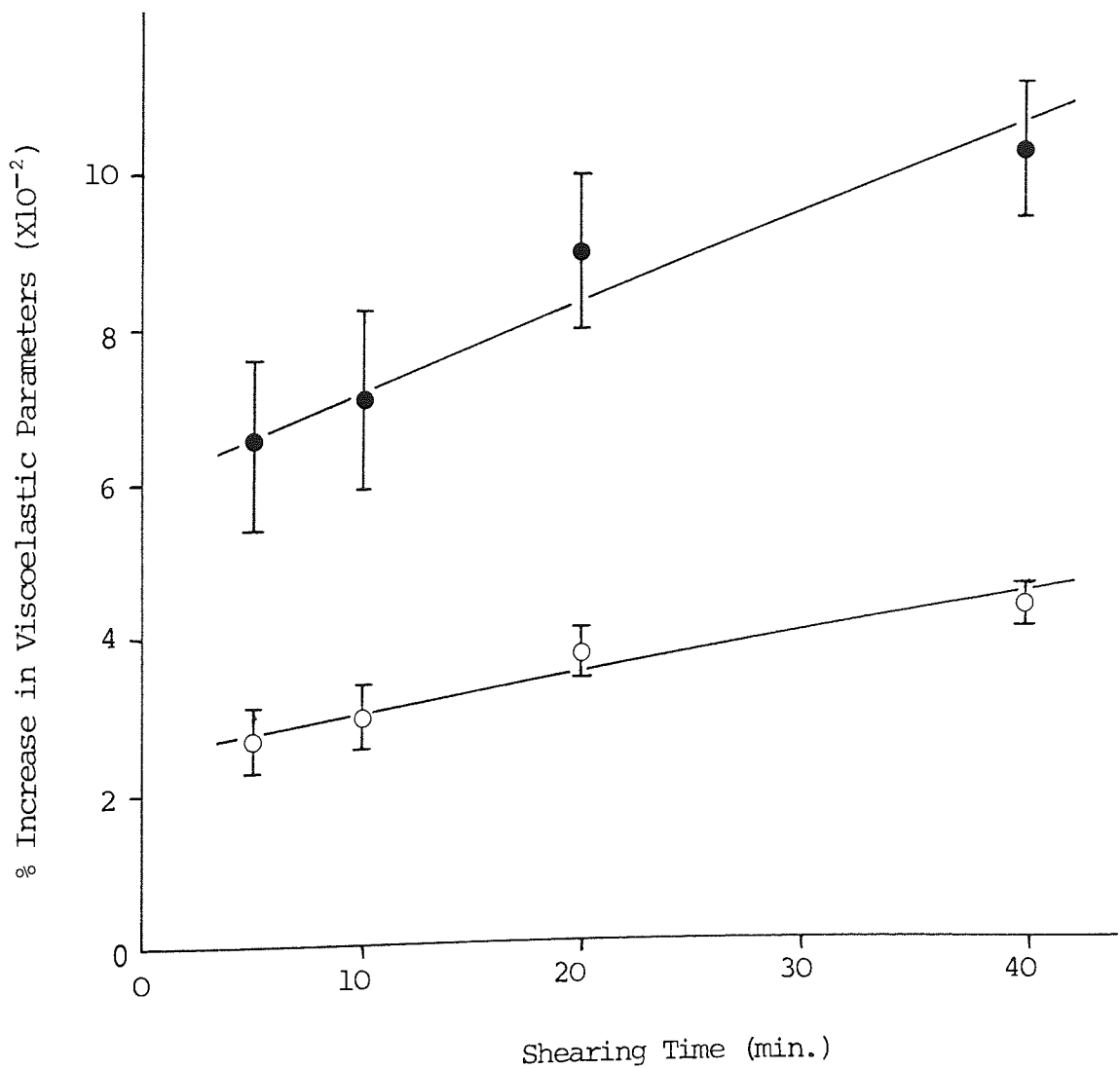
Figure 3.21. The Effect of the Frequency of Oscillation on the Dynamic Viscosity, η', and Storage Modulus, G', of Various Concentrations of Carbopol 934P Gels.

Carbopol Concentrations (% w/w) : 0.21 △,(Dynamic Viscosity) and 0.21 ○, 0.46 ◖,0.64 ◑,1.61 ●,(Storage Modulus).
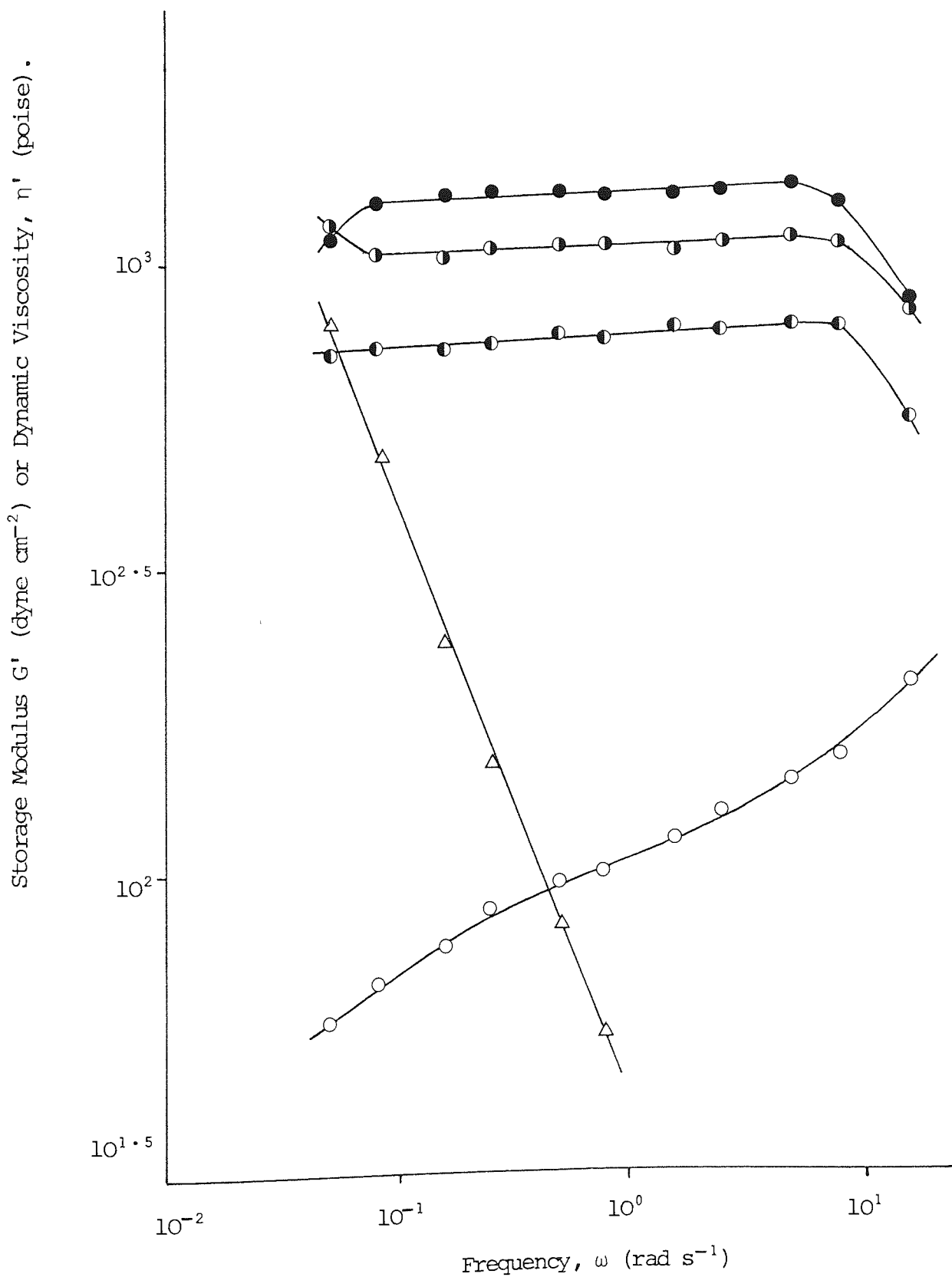
Figure 3.22. The Effect of the Concentration of
Carbopol 934P on the Storage Modulus, G', at
Oscillation Frequency, $\omega = 2.5$ rad s^{-1}.
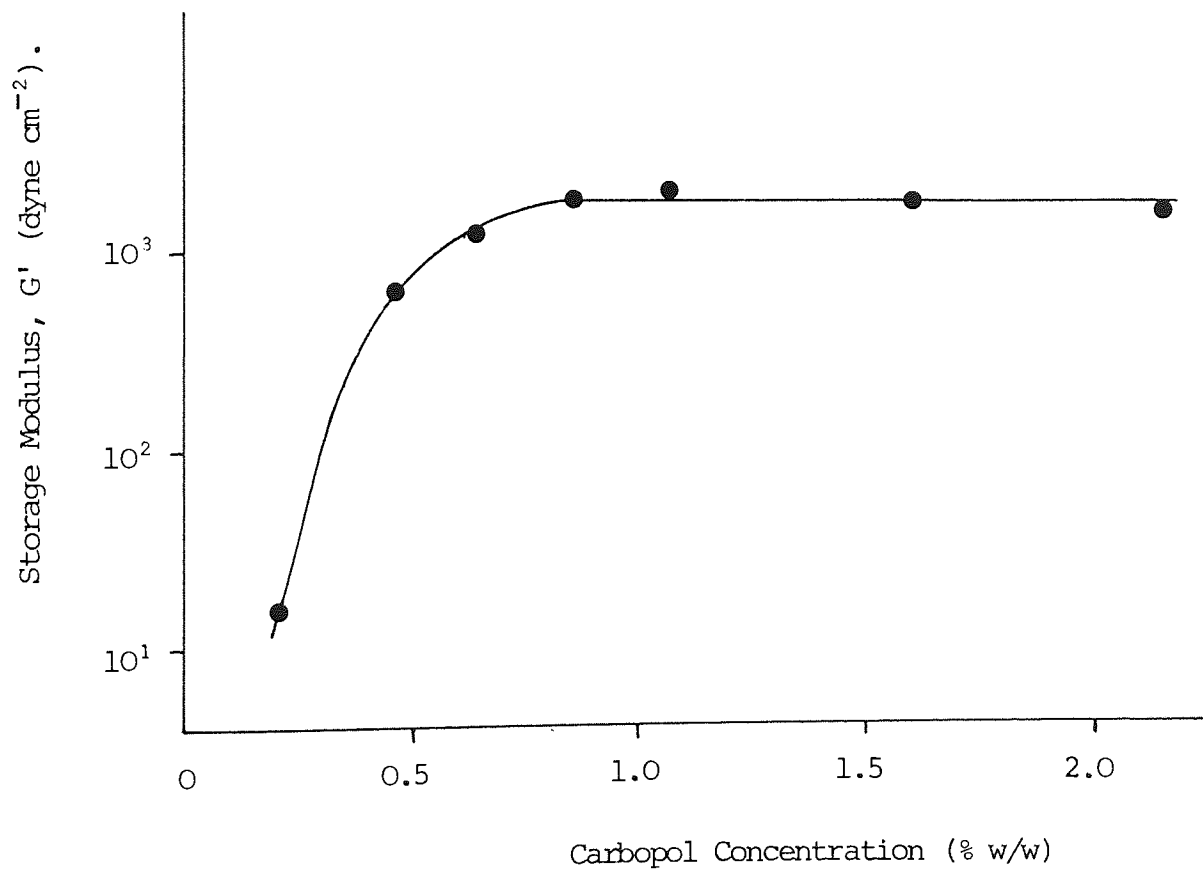
Figure 3.4.; the parameters f and b_V from the Shangraw expression, Equation 3.3., using continuous shear data gave a similar trend to G' but without such a plateau. These are plotted in Figure 3.23. The only η' (ω) line for Carbopol 0.2% w/w shown in Figure 3.21. has a high slope which suggests a very high η_0 value at a sufficiently low frequency. This line would move to lower frequencies with higher Carbopol concentrations making η' (ω) measurement difficult with the rheogoniometer. It is interesting that G' (ω) for Carbopol 0.2% and Xanthan 0.8% are roughly equivalent.

On addition of Alginate, in resemblance to Xanthan systems, G' (ω) is affected to a greater extent than η' (ω). This was quantified by using two approaches: (i) to increase the Carbopol concentration C_1 in the presence of Sodium Alginate 5% w/w, see Figures 3.24. to 3.26., and (ii) to increase the Alginate concentration C_2 in Carbopol 0.8% w/w, see Figures 3.27. to 3.29.. As would be expected, G' (ω) and η' (ω) increased in protocol (i) and decreased in (ii) but the ways in which they changed is significant. For protocol (i), increasing C_1 above 1.4% w/w had little effect upon η' (ω) but G' (ω) continued to rise significantly; the region of $C_1 \simeq 1.0\%$ w/w appeared to be most critical with respect to G' (ω) and η' (ω).

The corresponding continuous shear data for protocol (ii) is given in Figure 3.30. for η_∞ and f against C_2. This data shows only qualitative similarities with the oscillatory

Figure 3.23. The Effect of the Concentration of Carbopol 934P on the Continuous Shear Rheological Parameters: f ○ and b_v ●. (See Section 3.2.4. for an explanation of these terms).
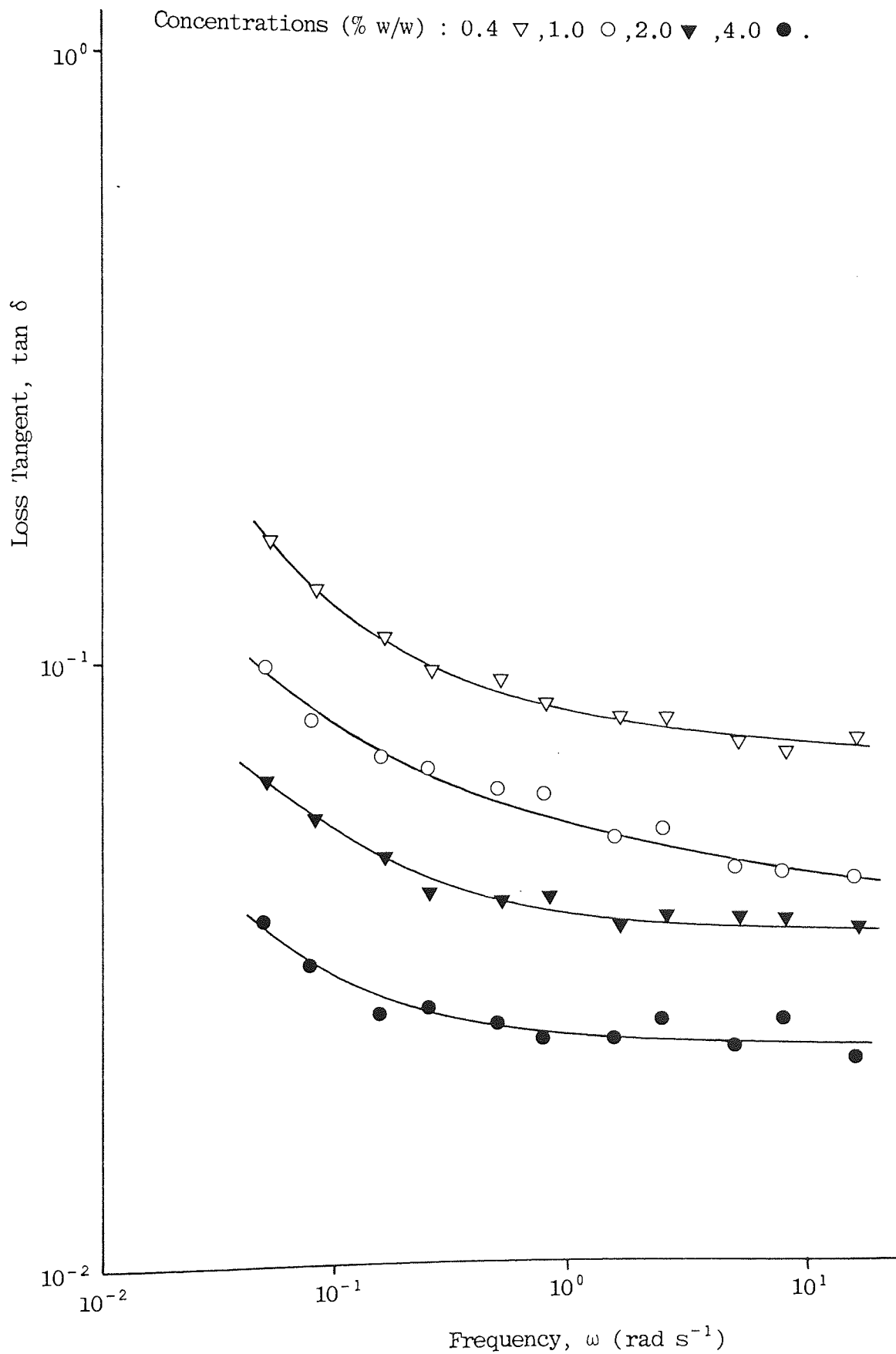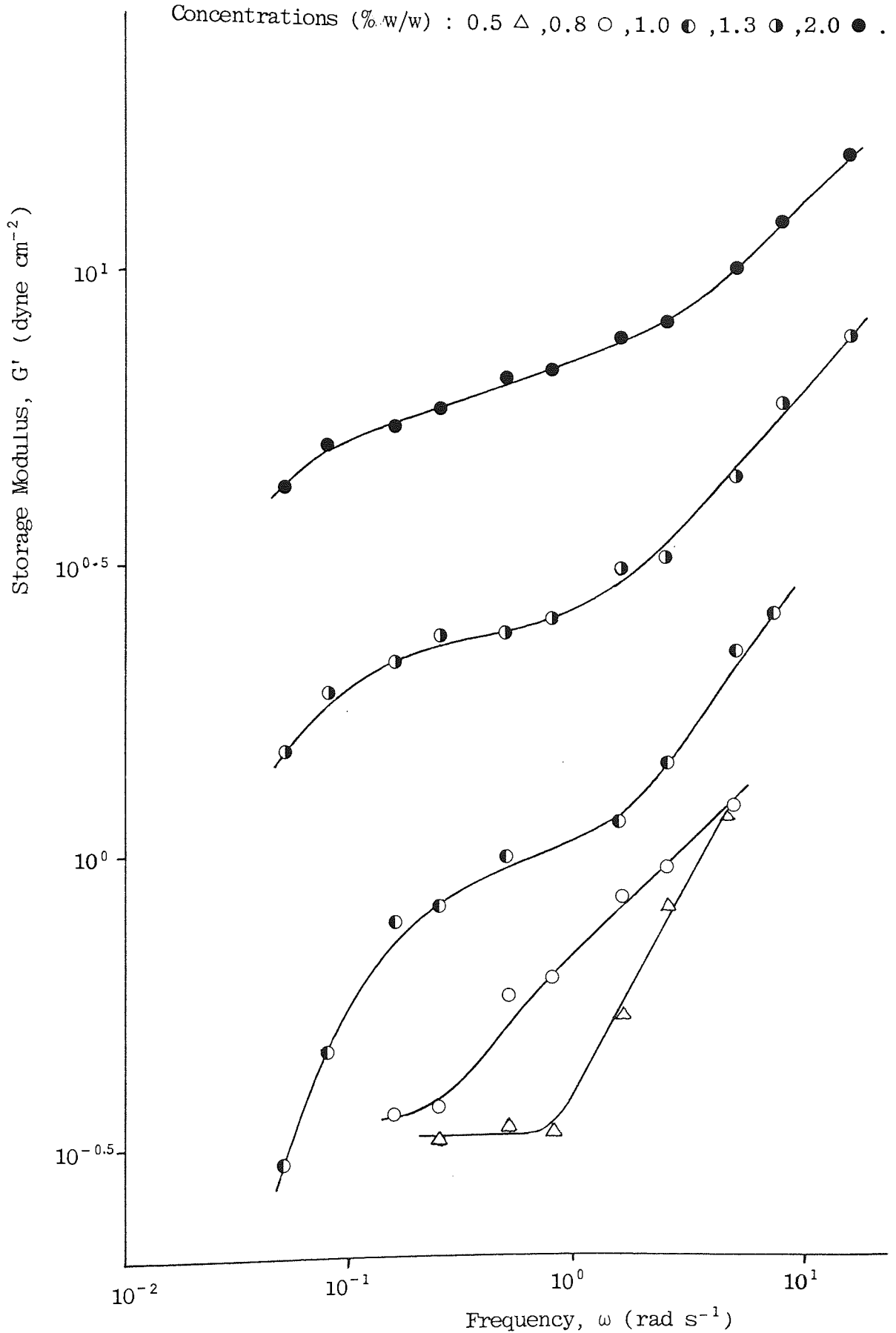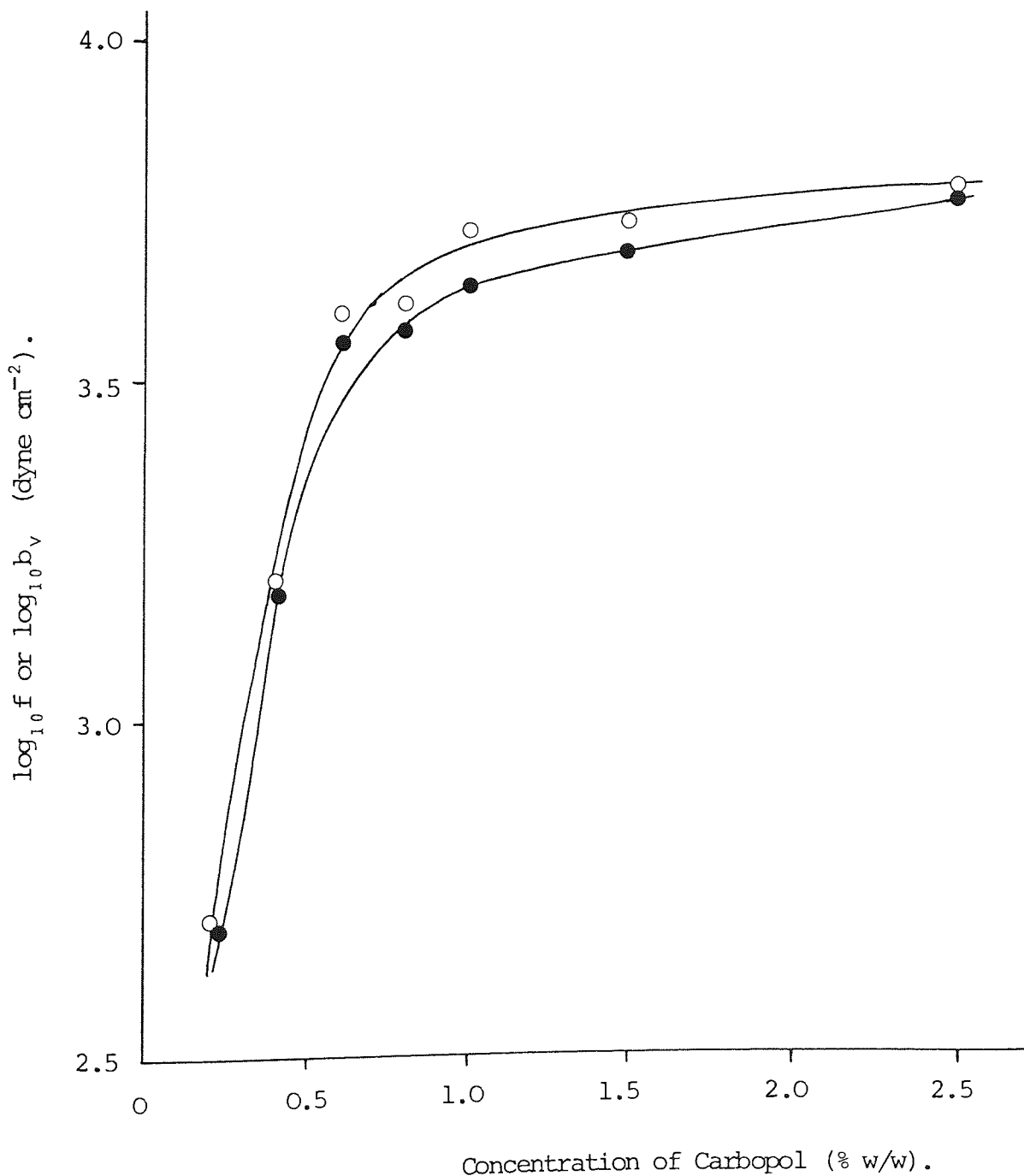
Figure 3.24. The Effect of the Concentration of Carbopol 934P in Sodium Alginate 3% w/w Solution on the Storage Modulus, G', plotted as a function of the Frequency of Oscillation, ω.

Carbopol Concentration (% w/w) : 0.6 ▽, 0.9 △, 1.1 ▲, 1.4 ▲, 1.6 ○, 1.8 ◑, 2.1 ◐, 2.4 ●.
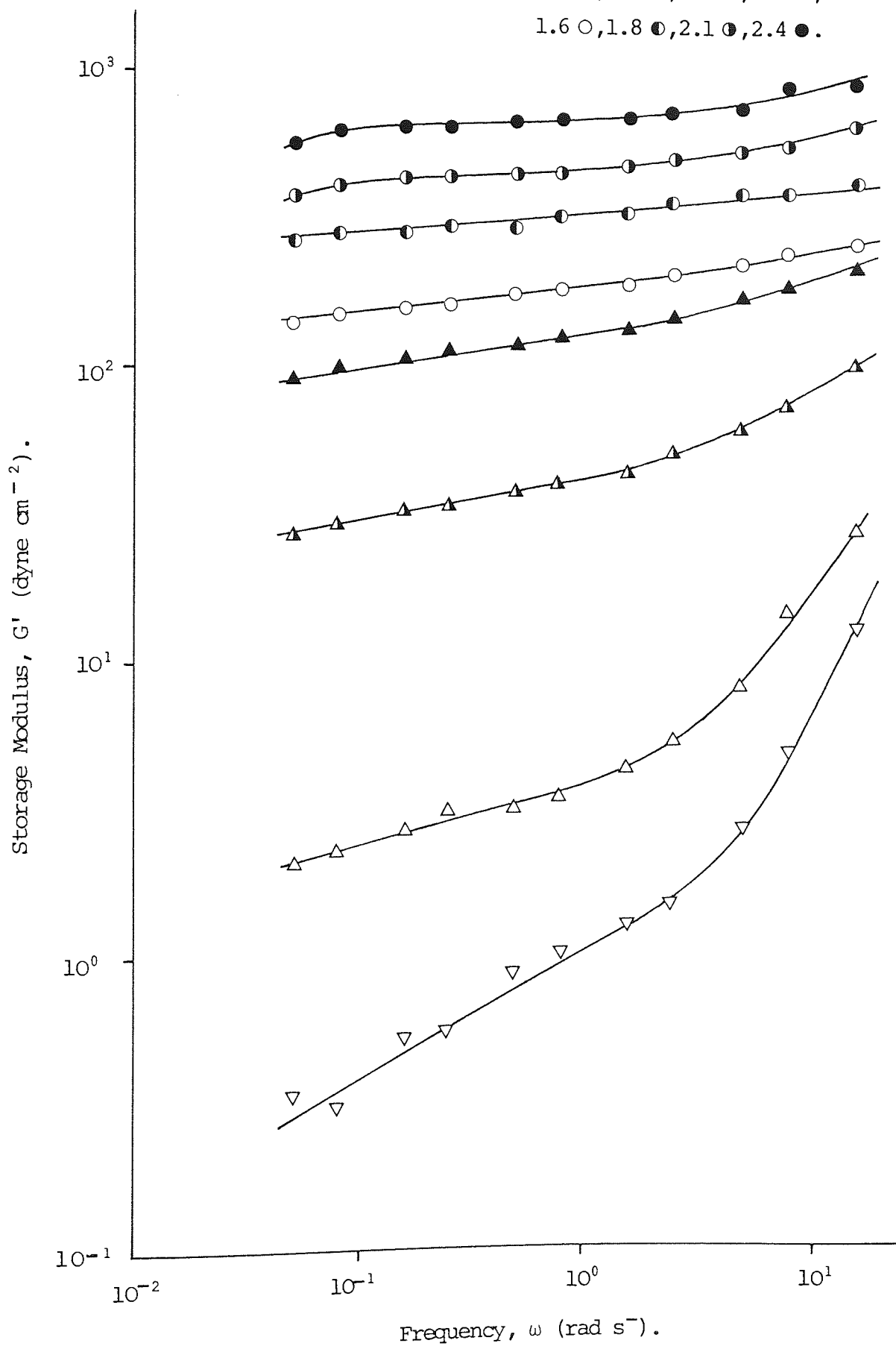
Figure 3.25. The Effect of the Concentration of Carbopol
in Sodium Alginate 3% w/w Solution on the Dynamic Viscosity,
η', plotted as a function of the Frequency of Oscillation, ω.

Concentrations (% w/w) : 0.6 ▽,0.9 △,1.1 ▲,1.4 ▲,1.6 ○,1.8 ◐.
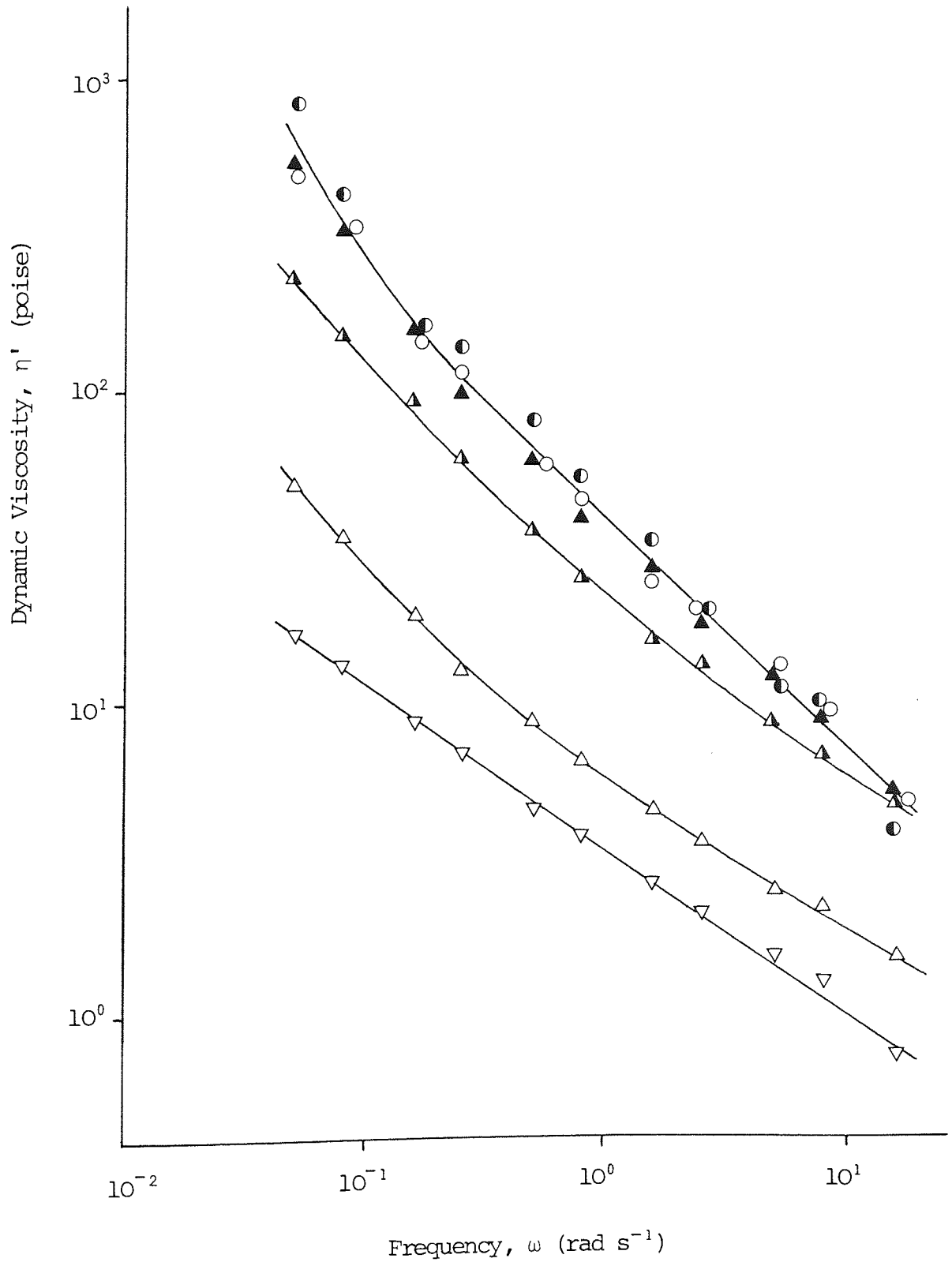
Figure 3.26. The Effect of the Concentration of Carbopol in Sodium Alginate 3% w/w Solution on (a) Storage Modulus and (b) Dynamic Viscosity at Oscillation Frequency $\omega = 2.5$ rad s^{-1}.
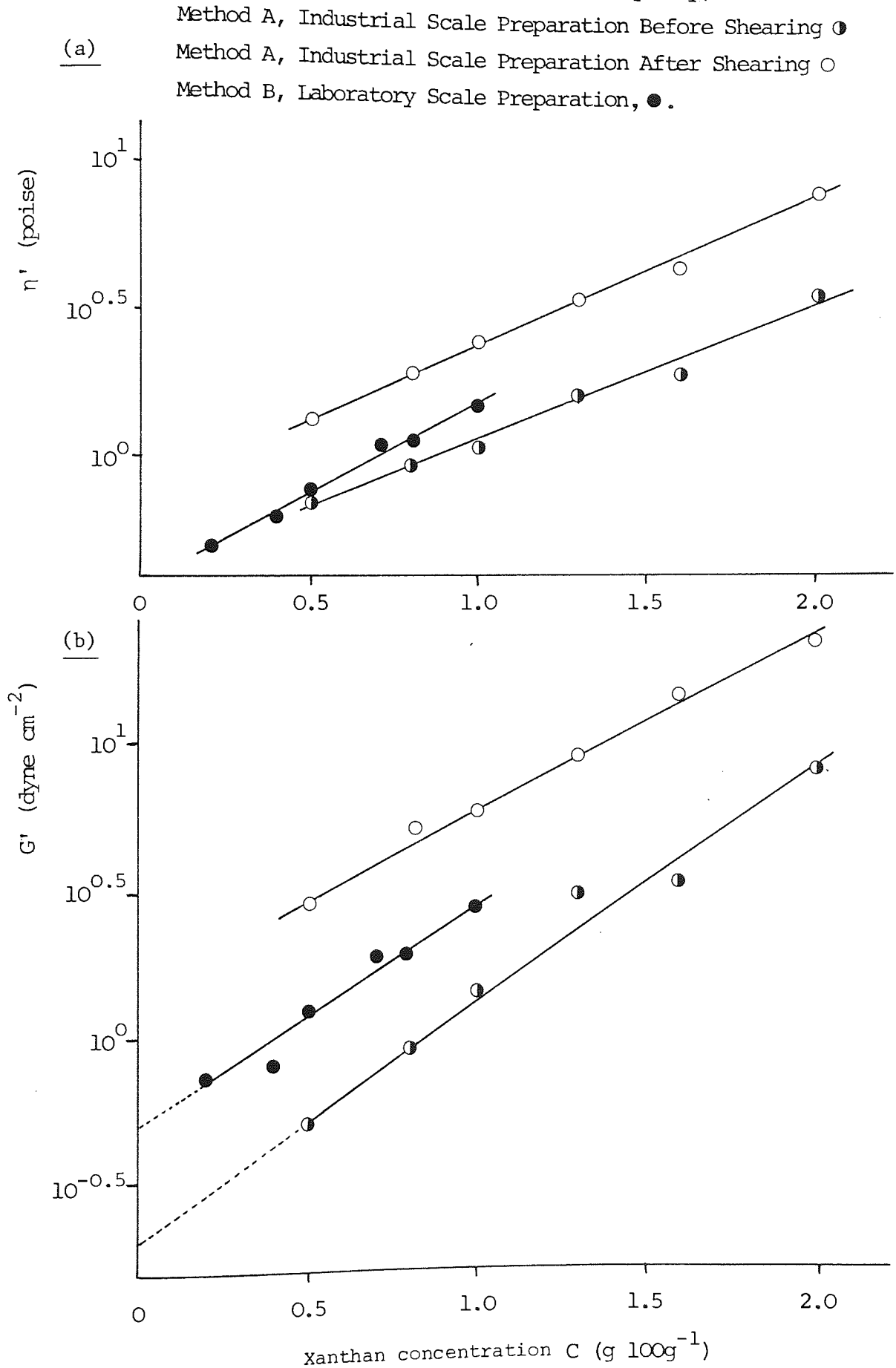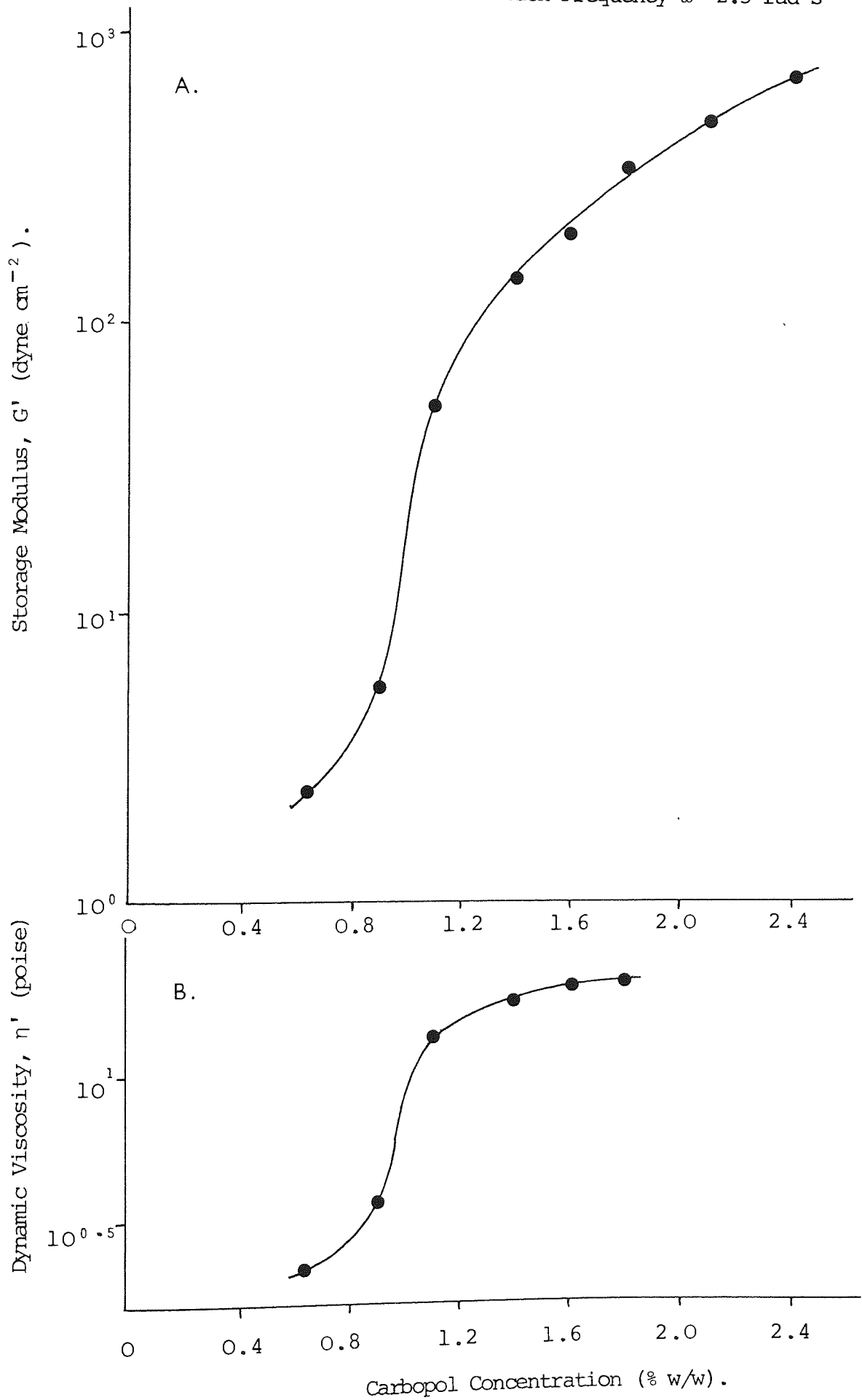
Figure 3.27. The Effect of the Concentration of Alginate in Carbopol 0.8% w/w Solution on the Storage Modulus, G', plotted as a function of the Frequency of Oscillation, ω . Concentrations (% w/w) : 0.5 ●,1.0 ◐,2.0 ◑,3.0 ○,4.0 ▲,5.0 △.
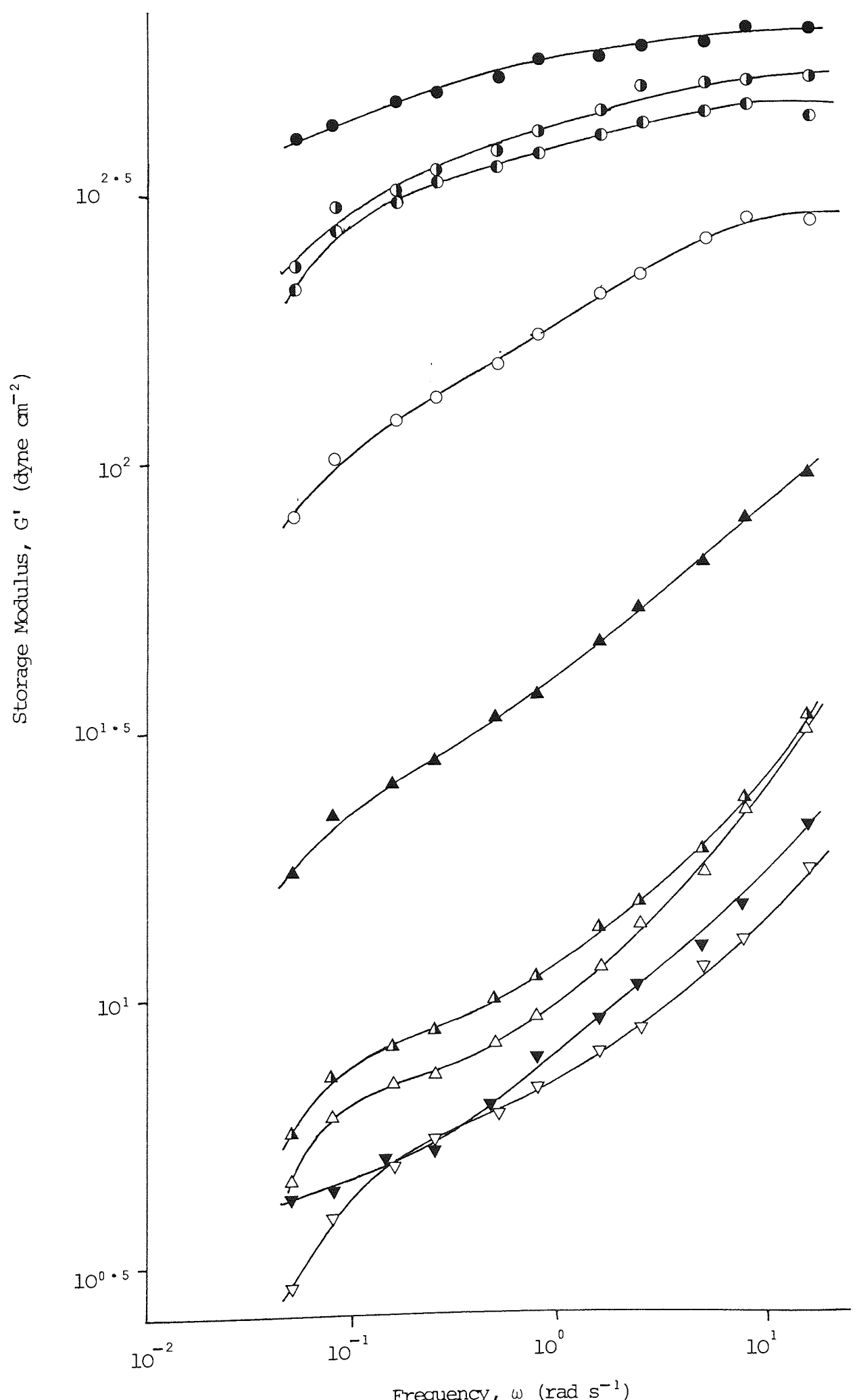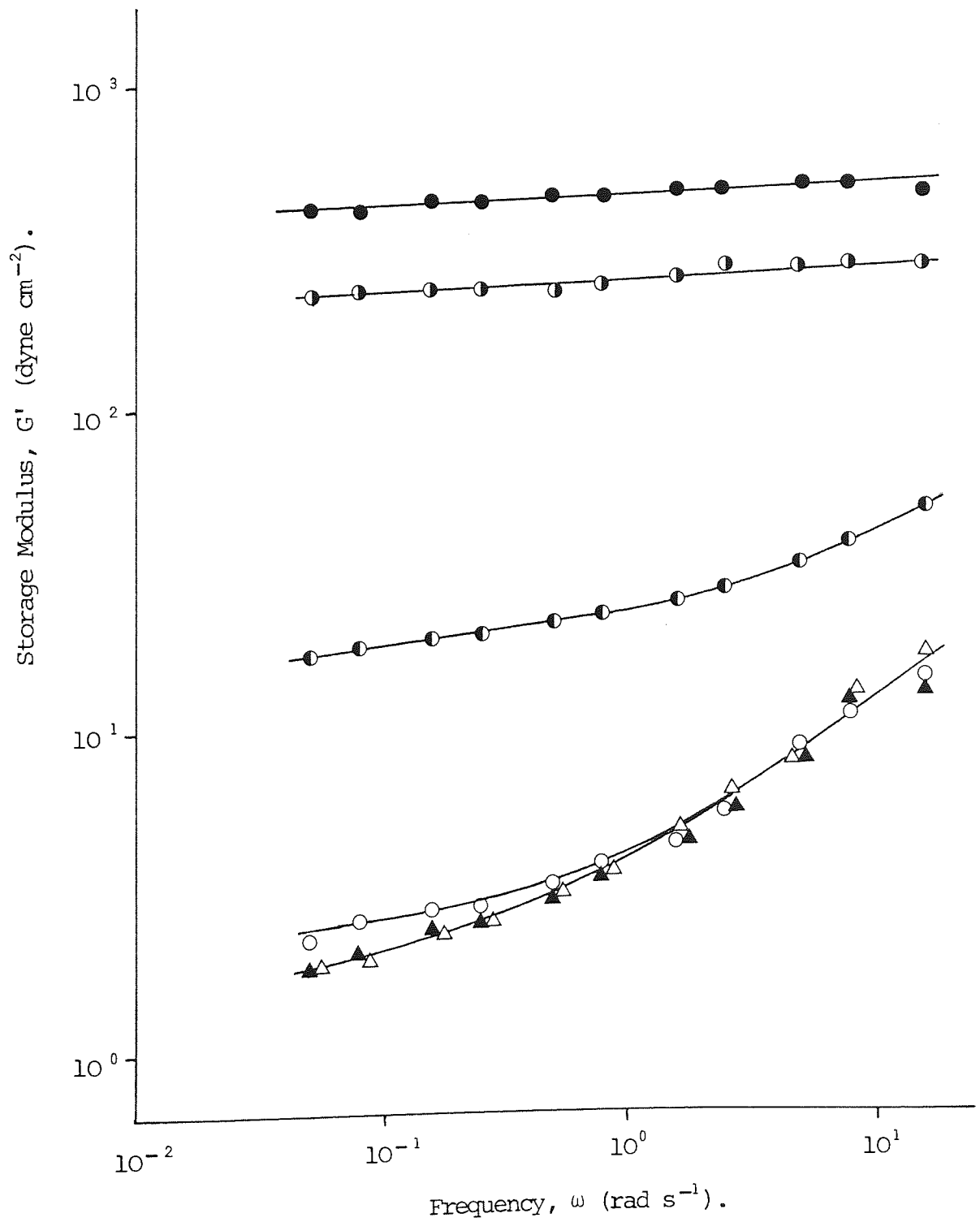
Figure 3.28. The Effect of the Concentration of Alginate in Carbopol 0.8% w/w Solution on the Dynamic Viscosity, η', plotted as a function of the Frequency of Oscillation, ω.

Concentrations (% w/w) : 1.0 ◑,2.0 ◕,3.0 ○,4.0 △.
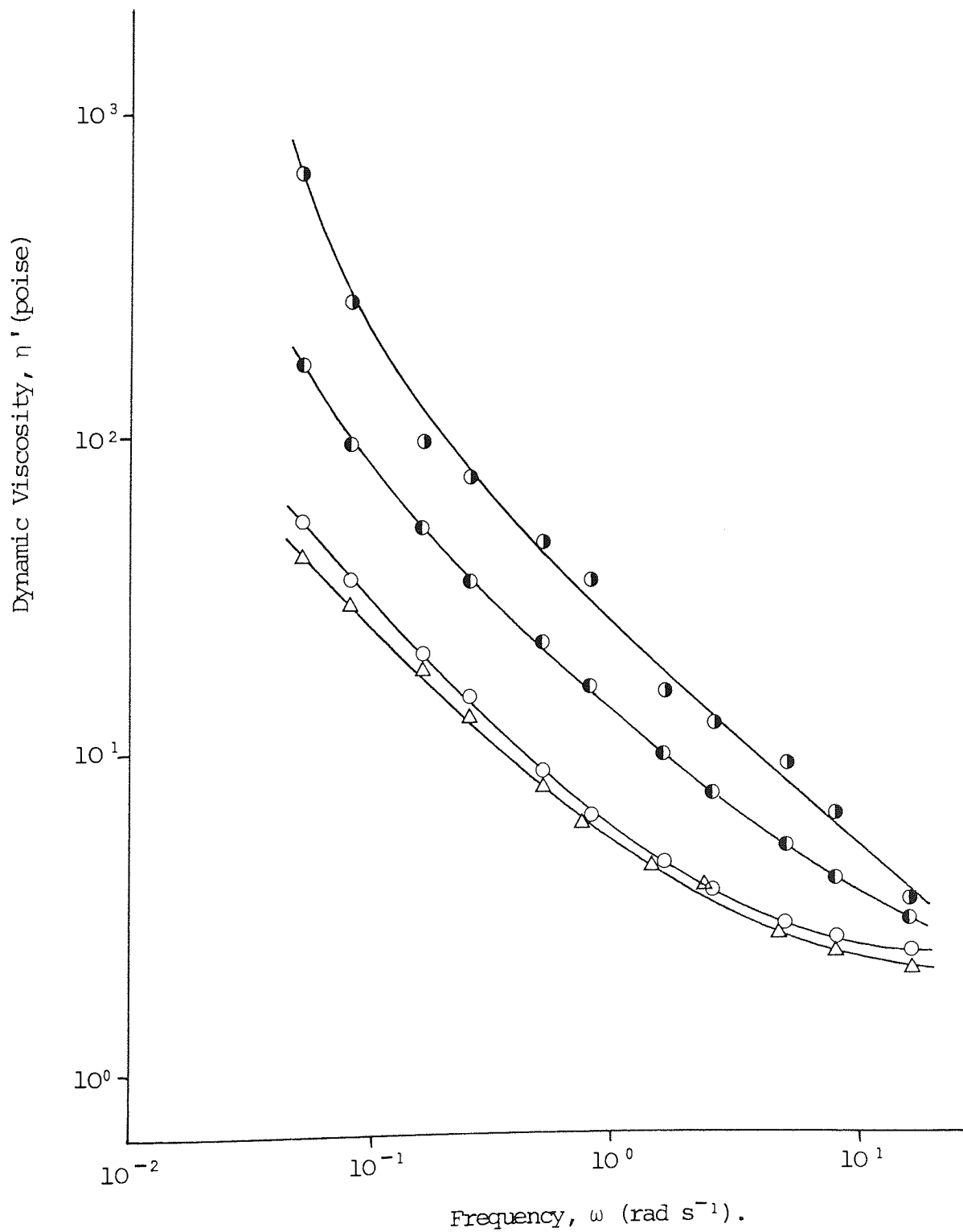
Figure 3.29. The Effect of the Concentration of Alginate in Carbopol 0.8% w/w Solution on (a) Storage Modulus and (b) Dynamic Viscosity at Oscillation Frequency $\omega = 2.5$ rad s^{-1} .
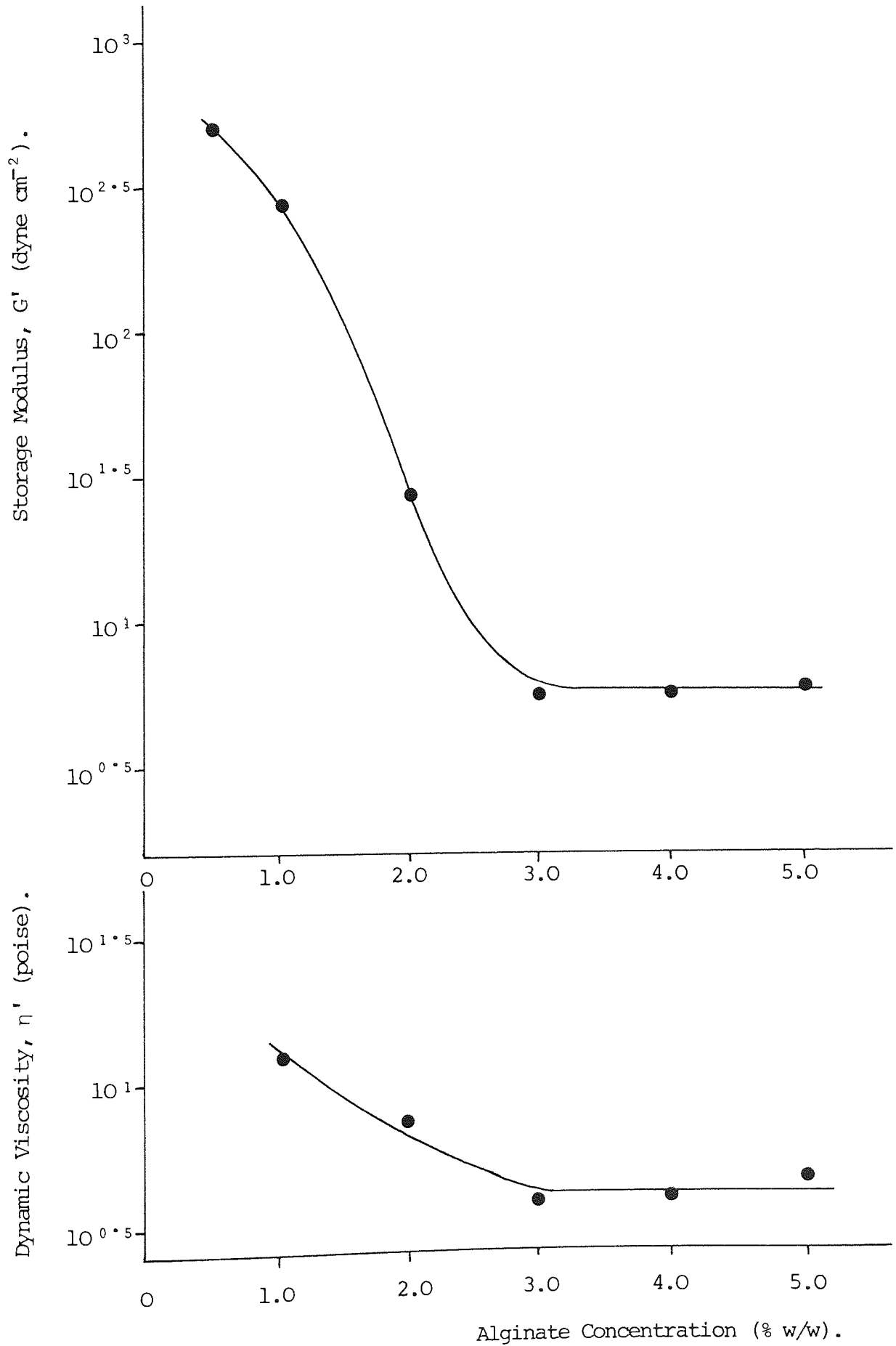
Figure 3.30. The Effect of the Concentration of Alginate in Carbopol 0.6% w/w Solution on the Continuous Shear Rheological Parameters (a) η_∞ and (b) f. For explanation of terms, see Section 3.2.4.

Sodium Alginate Concentration C_2 (% w/w).
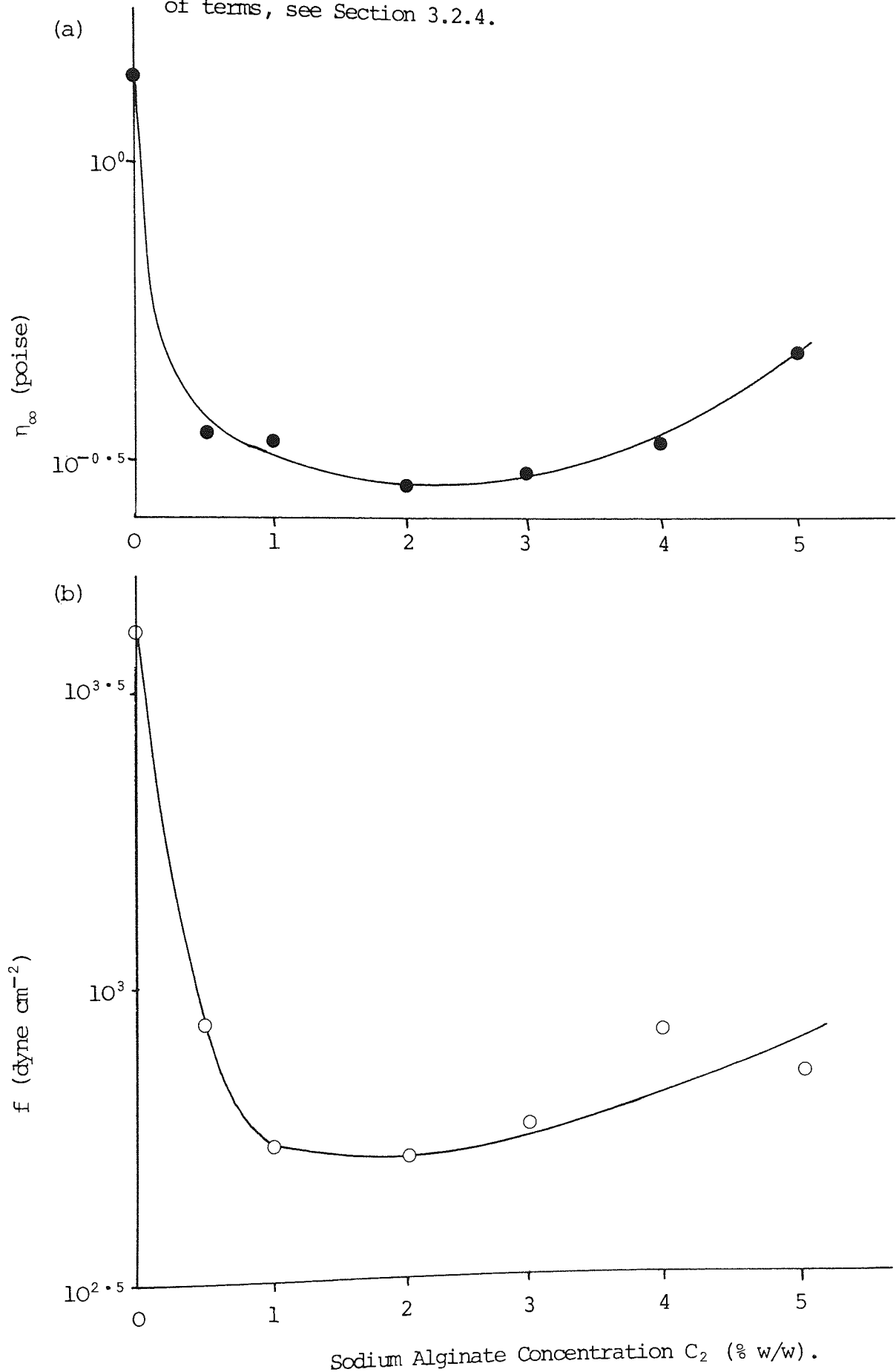
data in Figure 3.29.

3.4.2.2 Effect of Shearing

In attempts to measure the effect of shearing by the
'Silverson' high shear mixer on Carbopol systems, oscillatory
and continuous shear measurements were made. Samples of
Carbopol 0.6%, Carbopol 2.0% and Carbopol 2.0% with Alginate
5.0% were subjected to high shear for 10 min.. All
concentrations were w/w. Oscillatory measurements with the
usual regimens were taken at 24,48,96,192 and 264 hr. after
preparation. Due to siting of the apparatus, readings could
not be obtained before 24 hours had elapsed. There was no
significant difference in the viscoelastic parameters for low
or high shear samples throughout the 264 hr. period studied.

In order to obtain measurements within 24 hr. of preparation,
the continuous shear technique was employed. Samples of
Carbopol 0.6% alone, mixed with Alginate 0.5% and also with
Alginate 2.0% were sheared for up to 40 min. and $\tau - \dot{\gamma}$ curves
were obtained immediately after equilibration at 21.5^0 C. The
non-linear regression analysis estimates of f , η_∞ , b_V and
a are given in Table 3.2.; only Carbopol alone shows
significant shear breakdown (P > 0.999). This is illustrated

Table 3.2. Effect of Shearing Time on the Continuous Shear Rheological Parameters of Carbopol 0.6% w/w and the Effect of Alginate.

(a) Without Alginate

Shearing time (min)	f (dyne cm^{-2})	η_∞ (poise)	b_v (dyne cm^{-2})	a $\times 10^3$	$f - b_v$ (dyne cm^{-2})
0	4030	1.41	3670	7.35	360
10	2980	1.12	2690	6.12	290
15	2720	1.09	2570	9.06	150
20	2810	1.03	2460	4.31	350
25	2520	1.04	2340	8.57	180
30	3010	0.98	2620	3.26	390
40	2730	1.02	2430	4.33	300

(b) Alginate 0.5% w/w

0	880	0.35	830	4.37	50
5	780	0.31	750	3.89	30
10	860	0.33	830	3.13	30
15	790	0.34	760	3.20	30
20	850	0.31	780	2.50	70
30	830	0.30	800	2.83	30

(c) Alginate 2.0% w/w

0	507	0.28	473	1.55	34
5	524	0.25	513	1.82	11
10	439	0.22	440	2.02	0
15	441	0.24	438	1.88	3
20	461	0.25	446	2.10	15
30	458	0.30	458	1.92	0

in Figure 3.31., where the estimates of f, η_∞ and b_V are plotted against the shearing time. The apparent shear stability in the presence of Alginate is probably due to greater ease of realignment of polymer molecules when cross-linkages are largely absent.

Carbopol systems in the presence of Alginate did not manifest the sedimentation properties of the Xanthan gum systems either with or without high shear mixing. The storage of Carbopol – Alginate mixes prepared in distilled water, at temperatures of 20 to 50^0C for 6 months did not give rise to syneresis or phase separation.

3.4.3 Proprietary Preparations

Several proprietary oral liquid formulations including syrups, suspensions and an emulsion were tested in oscillatory shear with the same regimens as used in Sections 3.4.1. and 3.4.2.. The storage modulus G' (ω) and dynamic viscosity η' (ω) curves are given in Figures 3.32. to 3.35. where the logarithmic ordinate scale is adjusted in each Figure for clarification of the individual curves. The loss tangent $\tan \delta$ (ω) curves, termed the 'consistency spectra' by Davis [181] since they encompass both viscous and elastic effects, are given in Figures 3.36. and 3.37.. The proprietary preparations used are listed in Table 3.3..

Most noticeable in these curves is the extremely wide range of

Figure 3.31. The Effect of the Shearing Time of Carbopol 0.6% w/w Gel on the Continuous Shear Rheological Parameters (a) η_∞, (b) f ○ and b_v ●. For explanation of terms, see Section 3.2.4.
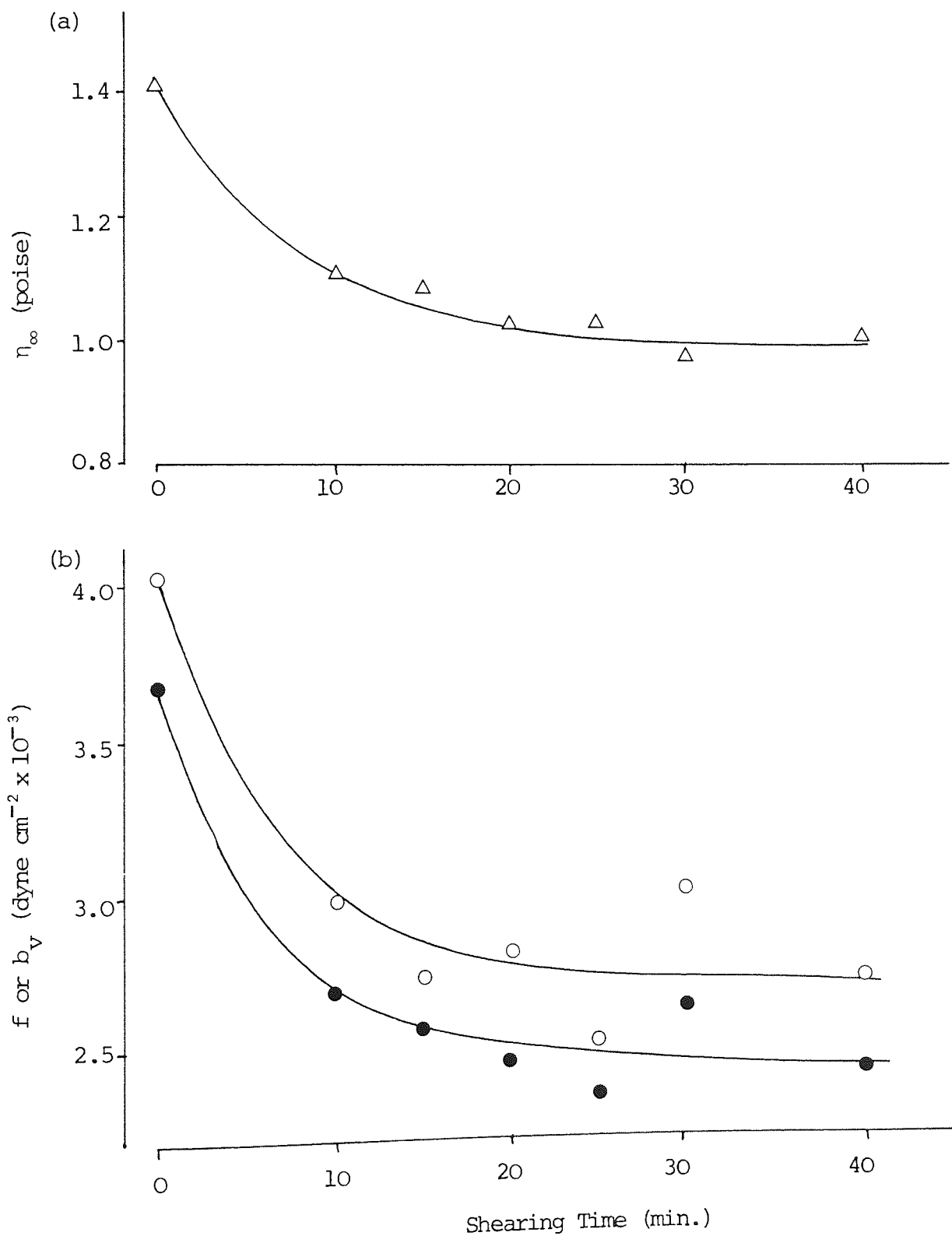
Figure 3.32. The Effect of the Frequency of Oscillation, ω, on the Storage Modulus, G', of Proprietary Oral Liquid Preparations.

Preparations : I ●,II ◐,III ◑,IV ○,V ▲,VI △,VII ▲, for Key, see Table 3.3.
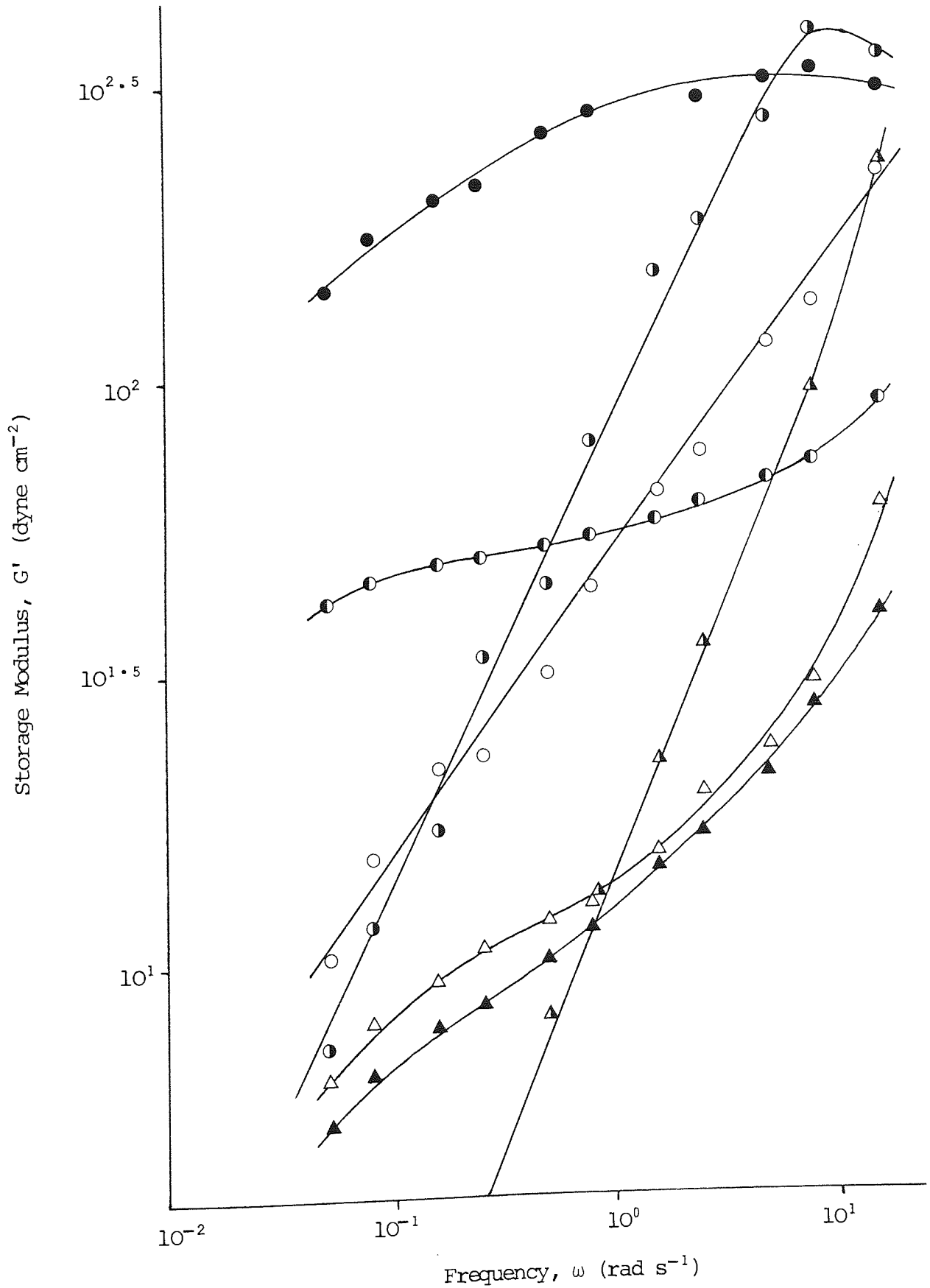
Figure 3.33. The Effect of the Frequency of Oscillation, ω, on the Storage Modulus, G', of Proprietary Oral Liquid Preparations.

Preparations : VIII ●,IX ◑,X ◑,XI ○,XII ▲,XIII ▲,

XIV △,XV ▽, for Key, see Table 3.3.

Figure 3.33. (see facing page)
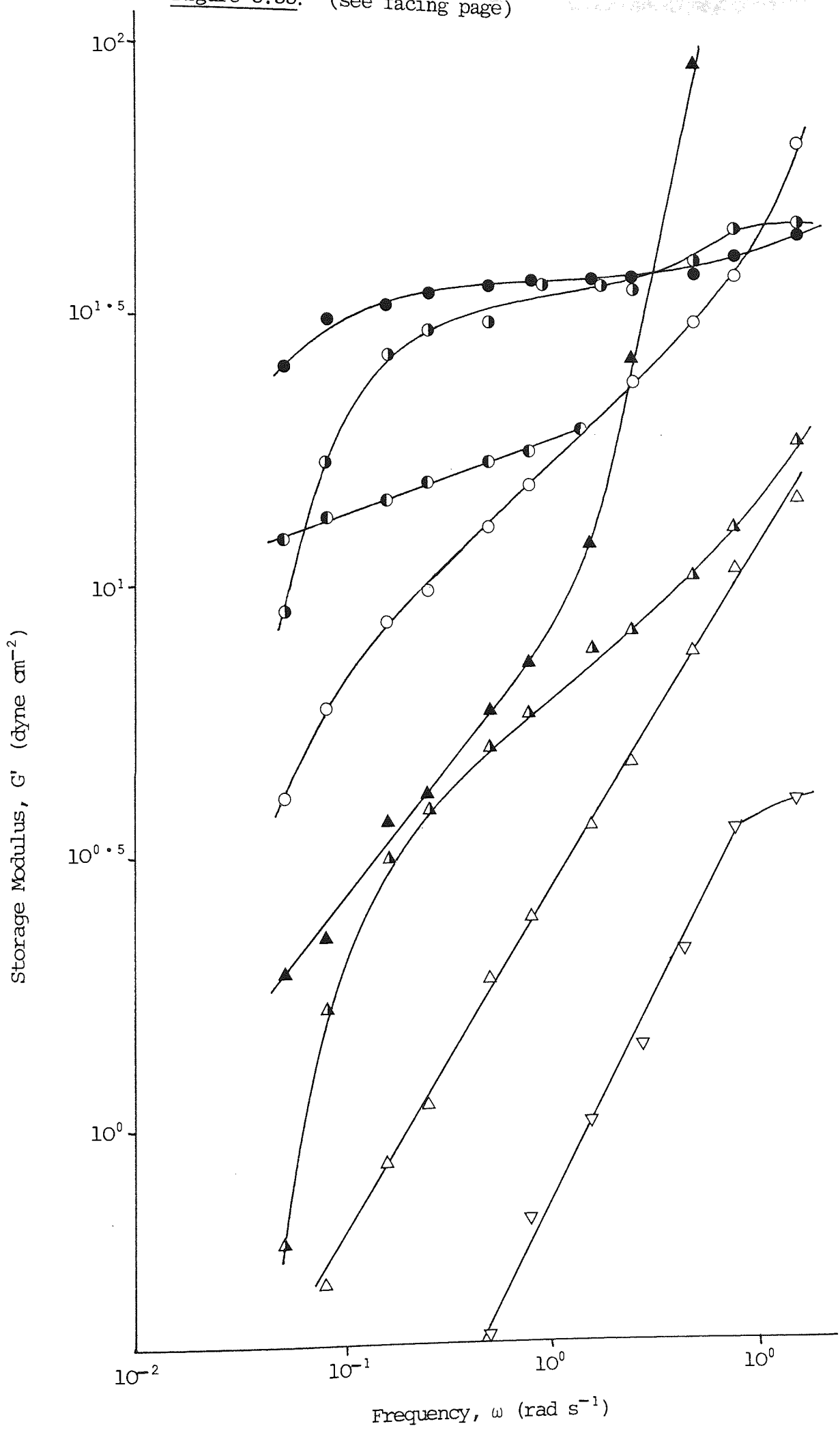
Figure 3.34. The Effect of the Frequency of Oscillation, ω, on the Dynamic Viscosity, η', of Proprietary Oral Liquid Preparations.

Preparations : I ●,II ◑,III ◑,IV ○,V ▲,VI △,VII ▲.

Figure 3.34   (see facing page)
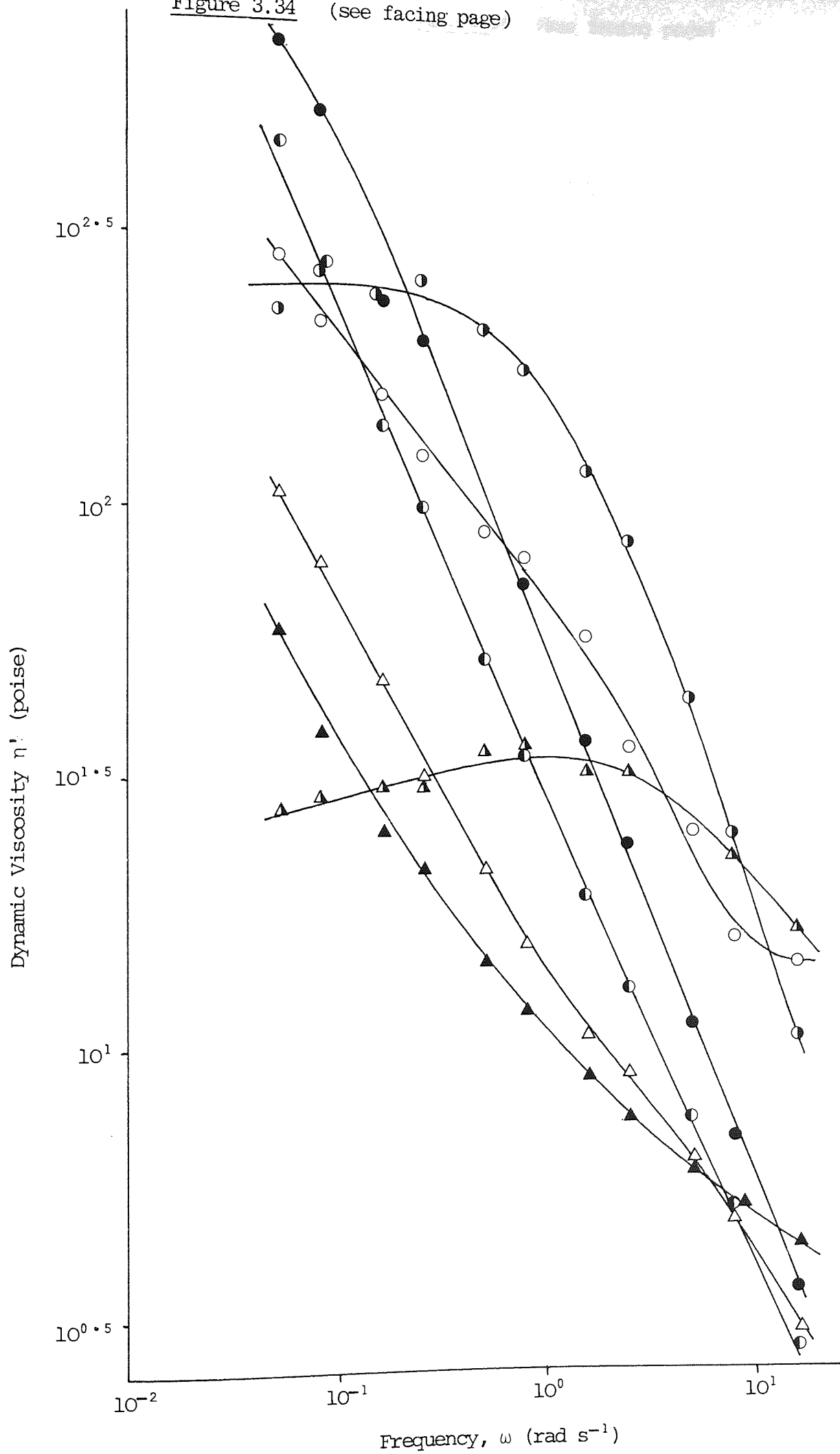
Figure 3.35. The Effect of the Frequency of
Oscillation, ω, on the Dynamic Viscosity , η',
of Proprietary Oral Liquid Preparations.

Preparations : VIII ●,IX ◑,X ◐,XI ○,XII ▲,
               XIII ▲,XIV △,XV ▽; for key,
               see Table 3.3.

Figure 3.35 (see facing page)

Dynamic Viscosity η' (poise)

Frequency, ω (rad s^{-1})

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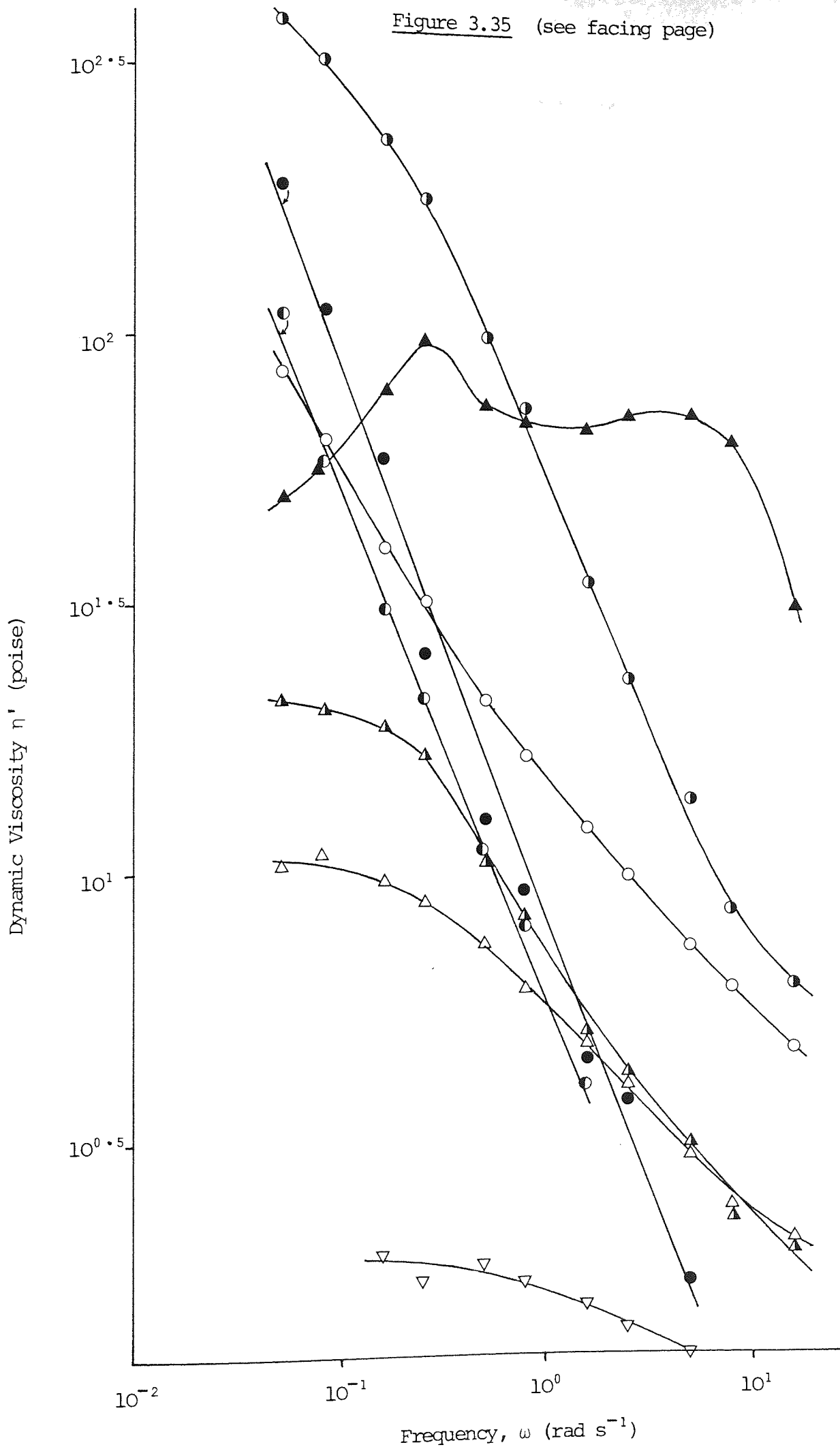
Figure 3.36. The Effect of the Frequency of Oscillation, ω, on the Loss Tangent, tan δ, of Proprietary Oral Liquid Preparations.

Preparations : I ●,II ◑,III ◑,IV ○,V ▲,VI △,VII ▲; For Key, see Table 3.3.
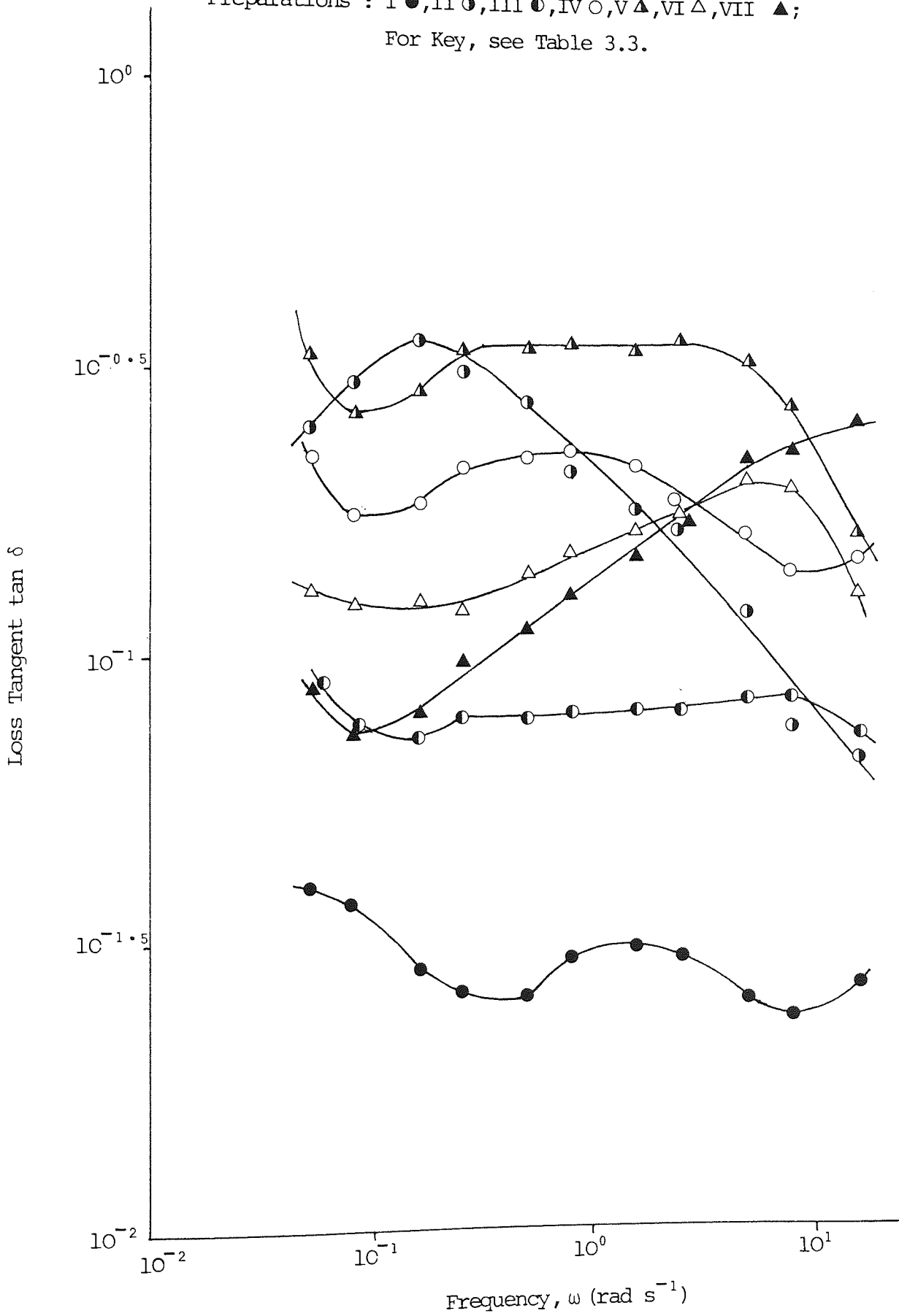
Figure 3.37. The Effect of the Frequency of Oscillation, ω, on the Loss Tangent, tan δ, of Proprietary Liquid Preparations.

Preparations : VIII ●, IX ◐, X ◑, XI ○, XII ▲, XIII ▲,
XIV △, XV ▽. For Key, see Table 3.3.
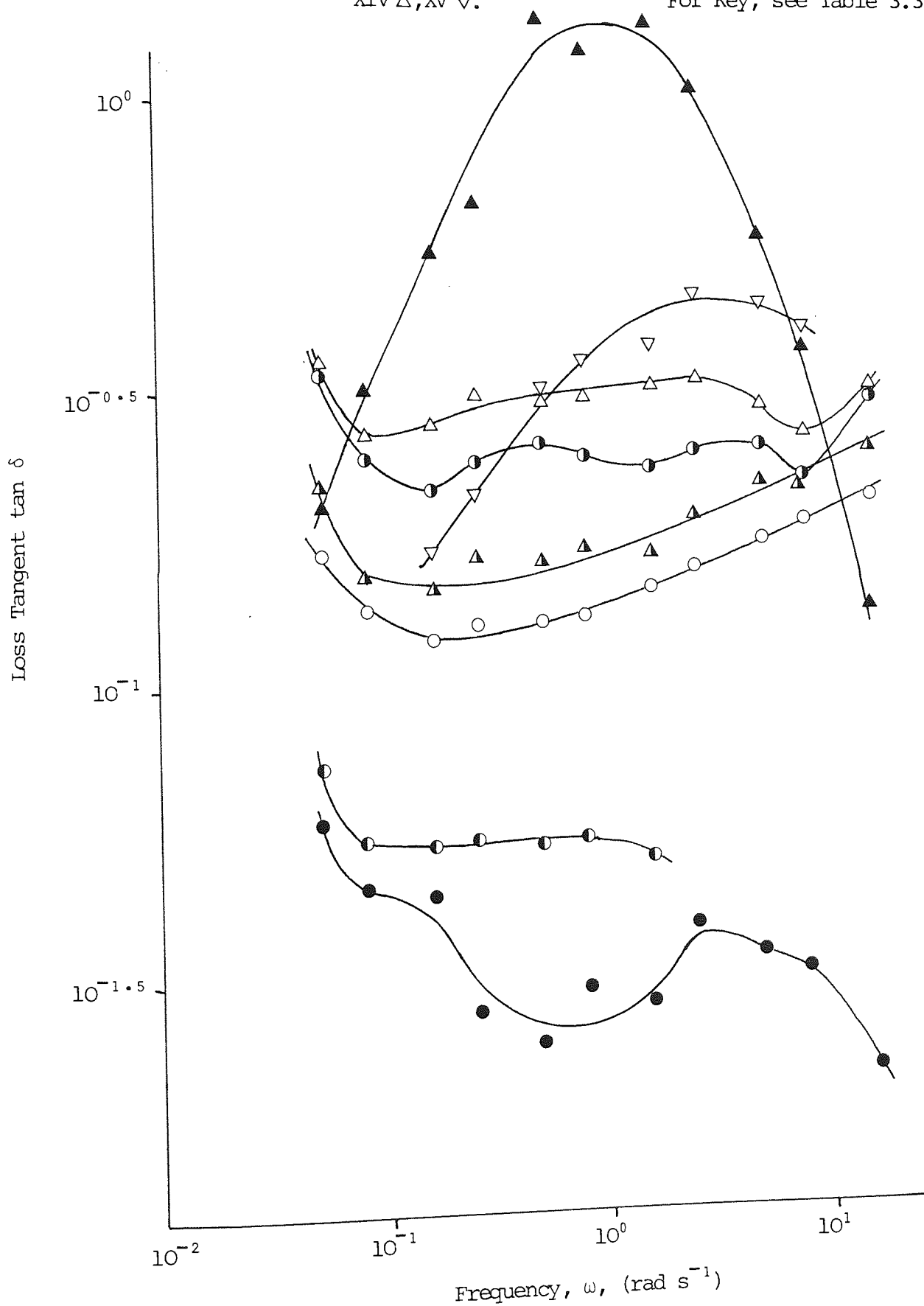
Table 3.3. Key to Figures 3.30. through 3.35. for Storage Modulus, Dynamic Viscosity and Loss Tangent curves of Proprietary Oral Liquid Preparations.

Reference Number	Commercial Name	Description	Manufacturer
I	'Pholtex'	Suspension	Riker Laboratories
II	'Andursil'	Suspension	Geigy Pharmaceuticals
III	'Furadantin'	Suspension	Eaton Laboratories
IV	'Agarol'	Emulsion	William Warner
V	'Fabahistin'	Suspension	Bayer UK.
VI	'Liquid Gaviscon'	Suspension	Reckitt and Colman
VII	'Pholcolix'	Syrup	William Warner
VIII	'Naprosyn'	Suspension	Syntex Pharmaceuticals
IX	'Mucaine'	Suspension	Wyeth Laboratories
X	'Dorbanex'	Suspension	Riker Laboratories
XI	'Calpol'	Suspension	Wellcome Foundation
XII	'Vi-Daylin'	Syrup	Abbott Laboratories
XIII	'Furoxone'	Suspension	Eaton Laboratories
XIV	'Tegretol'	Syrup	Geigy Pharmaceuticals
XV	'Juvel'	Syrup	Bencard

values of G', η' and tan δ exhibited, often varying by over

two powers of ten at any one frequency. With regard to Figures

3.32. and 3.33., there appears to be little correlation between

G' (ω) and either formulation type or subjective assessments

of the preparations. Theoretically, G' will approach zero at

low frequencies and many G' (ω) curves have high slopes,

each indicative of a low elastic contribution to consistency.

The G' (ω) curves with high slopes are found to have the

highest tan δ (ω) values shown in Figures 3.36. and 3.37..

Several preparations, notably II, V, XIII, XIV and XV showed

the tendency to plateau at low frequencies, thereby providing

estimates of η_0 , the zero shear viscosity. With a knowledge

of the mean particle size, R, the densities of the disperse

and continuous phases, ρ and ρm respectively, and the close

packing fraction, p, the settling rate of the suspension can be

calculated from η_0 using the equation of Buscall et al (40):

$$\frac{U}{U_0} = \left(1 - \frac{\phi}{P}\right)^{kp} \qquad 3.4$$

where U_0 =   sedimentation velocity of a single spherical
                     particle in a gravitational field from Stokes'
                     Law with $U_0 = \dfrac{2R^2 (\rho - \rho m)g}{9\eta_0}$ 3.5

           U =   rate of settling of suspension in a non-
                     Newtonian medium.

           ϕ =   volume fraction of disperse phase

           k =   constant, found to be 5.4 by Buscall et al (40)
                     but values of 5.1 (182), 5.0 (183), 6.55 (184)
                     and 5.8 (185) have been proposed.

Therefore, for separation to be avoided during the

manufacturer's shelf life of the product, η_0 should be chosen such that U is negligibly small.

The tan δ (ω) curves, or consistency spectra, may be expected to be useful since they combine elastic and viscous components. However, in practice (see Figures 3.36. and 3.37.), they appear to be of little use for the following reasons:

(i) Any systematic errors in G' and η' are compounded in order to obtain tan δ .

(ii) Values of tan δ cover a narrower range then either of the components it contains, thereby reducing the resolution between curves.

(iii) Tan δ values do not appear to show any correlation with any other suspension formulation variables.

Three different batches of formulation XI were tested on three separate occasions yielding the raw data of ν and C given in Table 3.4.. The reproducibility obtained reflects the reliability of both the measuring system and the formulation.

In order to look at the rôle of oscillatory testing as a quality control tool, samples of a suspension, XI, and an emulsion, IV, were stored at 50^0C for a short period. The G' (ω) and η' (ω) curves of Figures 3.38. to 3.41. show considerable changes during 39 days storage; approximately one logarithmic cycle in the case of product XI. This serves to illustrate that sensitive rheological measurements yielding fundamental parameters are capable of exposing any physical instability in the early stages of storage testing.

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Table 3.4. Reproducibility of Amplitude Ratio and Phase Angle
measurements of Three Batches of 'Calpol'
Suspension in Oscillatory Shear.

(a) Amplitude Ratio, ν.

Frequency (rad s^{-1})	Batch		
	1	2	3
0.0497	0.0318	0.0361	0.0364
0.0792	0.0413	0.0491	0.0462
0.157	0.0563	0.0673	0.0615
0.249	0.0681	0.0767	0.0739
0.497	0.0880	0.0979	0.0947
0.792	0.107	0.116	0.116
1.57	0.139	0.154	0.156
2.49	0.167	0.187	0.193
4.97	0.225	0.253	0.268
7.92	0.286	0.325	0.344
15.7	0.484	0.539	0.570

(b) Phase angle, C   (Rad)

Frequency (rad s^{-1})	Batch		
	1	2	3
0.0497	0.822	0.770	0.794
0.0792	0.725	0.663	0.641
0.157	0.679	0.556	0.586
0.249	0.654	0.619	0.642
0.497	0.624	0.589	0.661
0.792	0.613	0.617	0.642
1.57	0.635	0.646	0.673
2.49	0.648	0.659	0.677
4.97	0.654	0.649	0.682
7.92	0.627	0.627	0.656
15.7	0.518	0.472	0.469

Figure 3.38. The Effect of Aging time at 50°C on
the Storage Modulus, G' of Formulation XI plotted
as a function of the Frequency of Oscillation, ω.
Aging time (days) : 0 ●,7 ◑,14 ◐,24 ○,31 △,39 ▲.
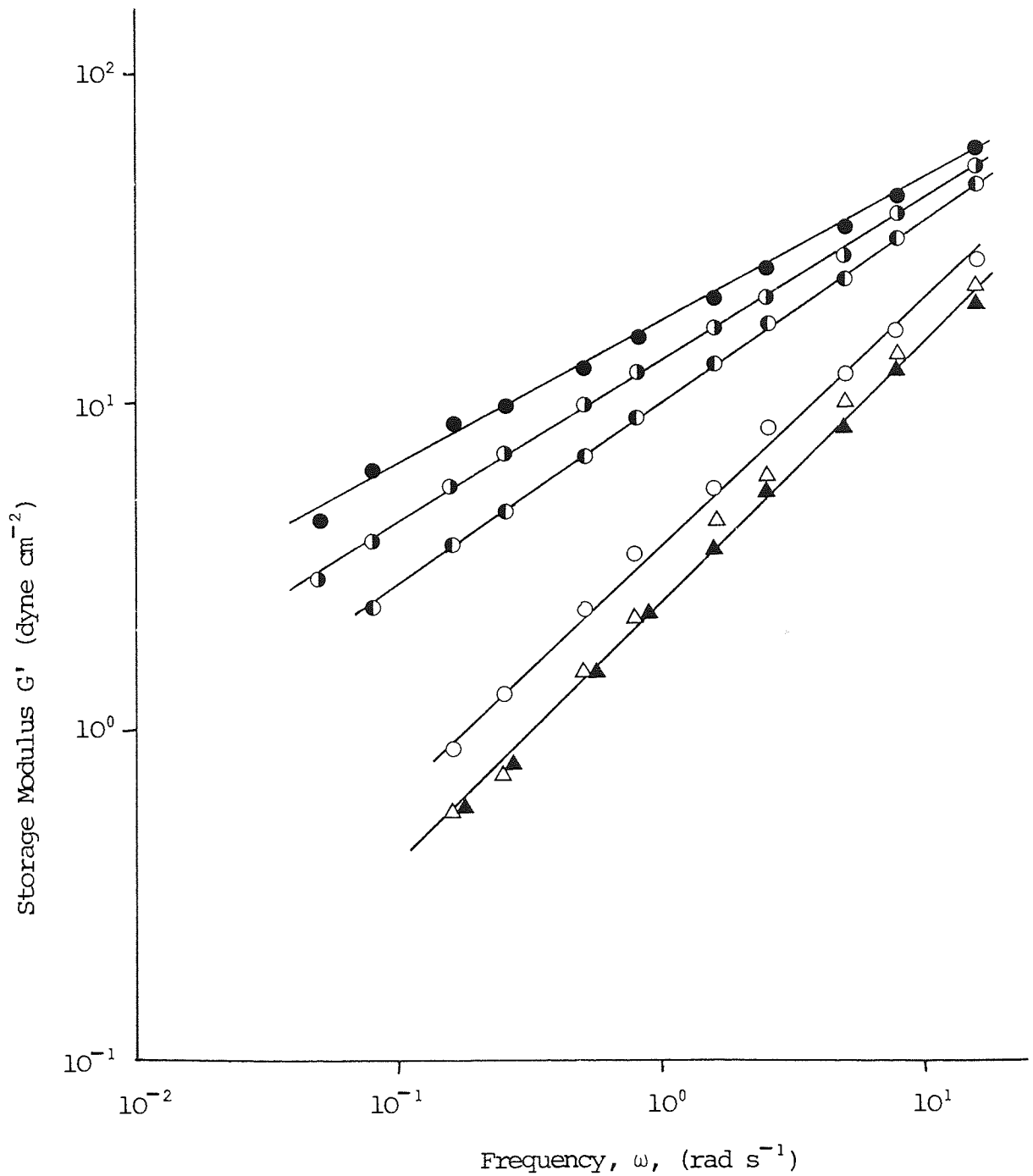
Figure 3.39. The Effect of Aging time at 50°C on the Dynamic Viscosity, η', Formulation XI plotted as a function of the Frequency of Oscillation, ω.

Aging time (days) : 0 ●,7 ◑,14 ◐,24 ○,31 △,39 ▲.
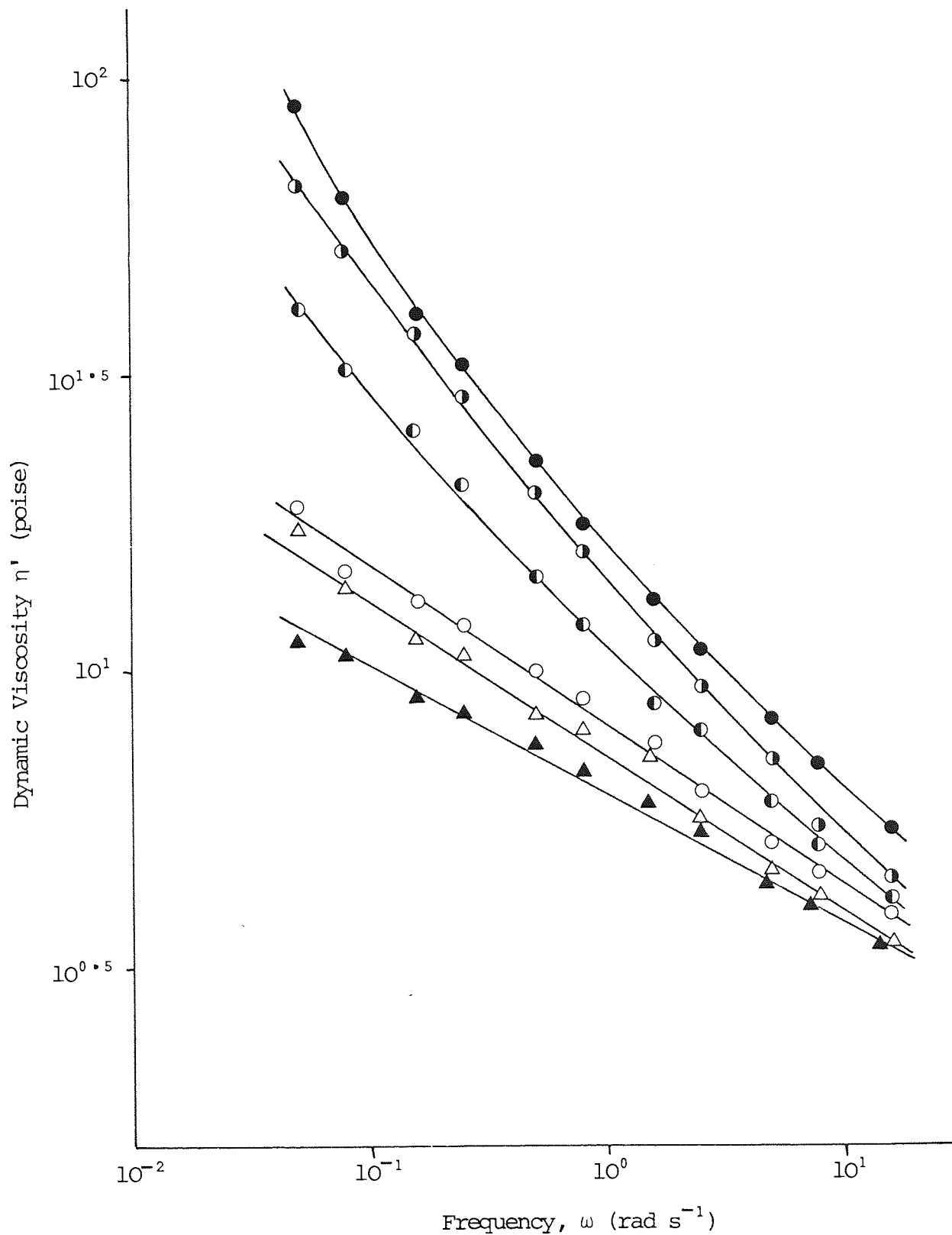
Figure 3.40. The Effect of Aging time at 50°C on the Storage Modulus, G', of Formulation IV plotted as a function of the Frequency of Oscillation, ω.

Aging time (days) : 0 ●, 7 ◑, 14 ◑, 24 ○.
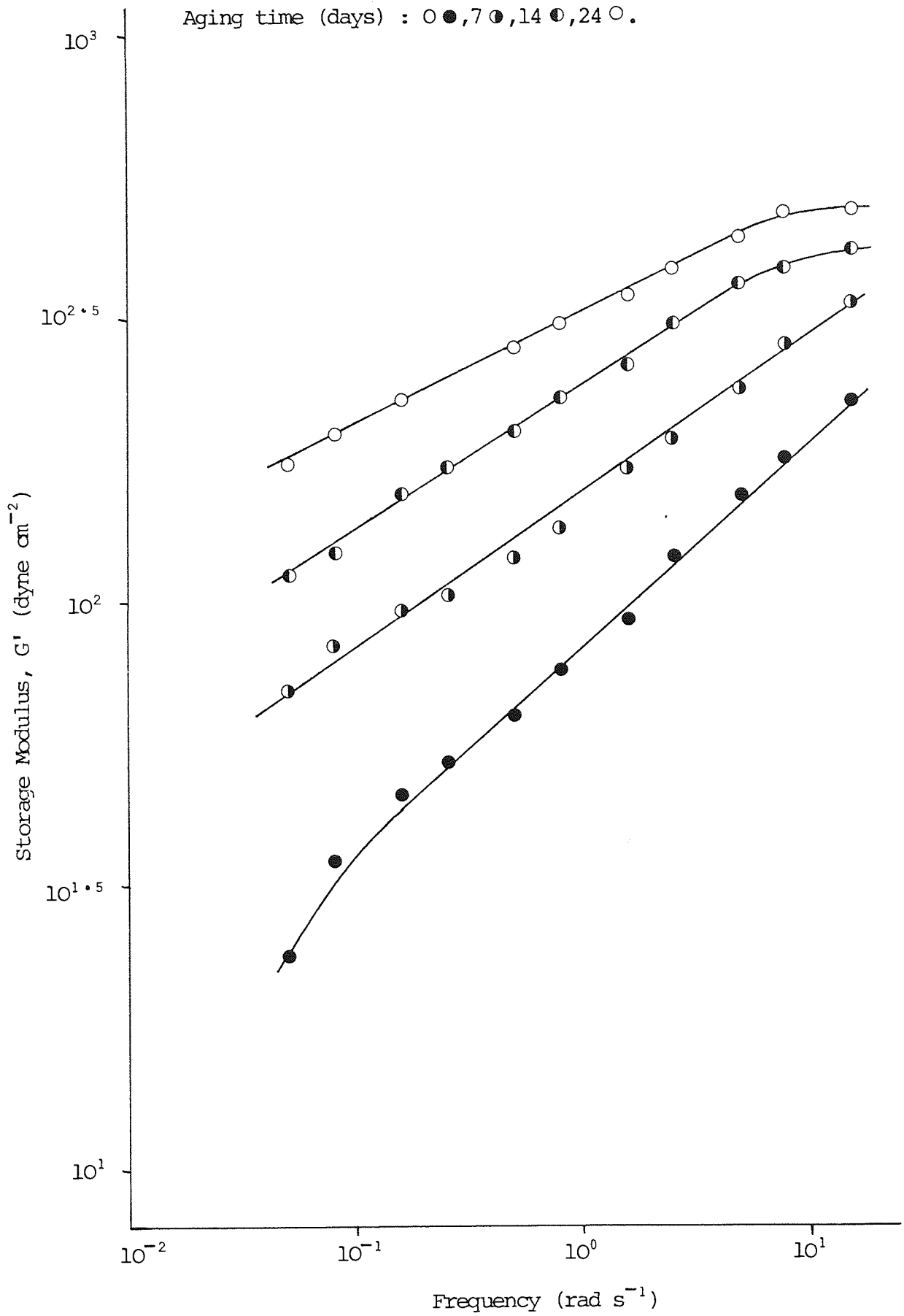
Figure 3.41. The Effect of Aging time at 50°C on the Dynamic Viscosity, η', of Formulation IV plotted as a function of the Frequency of Oscillation, ω.

Aging time (days) : 0 ●, 7 ◑, 24 ○.
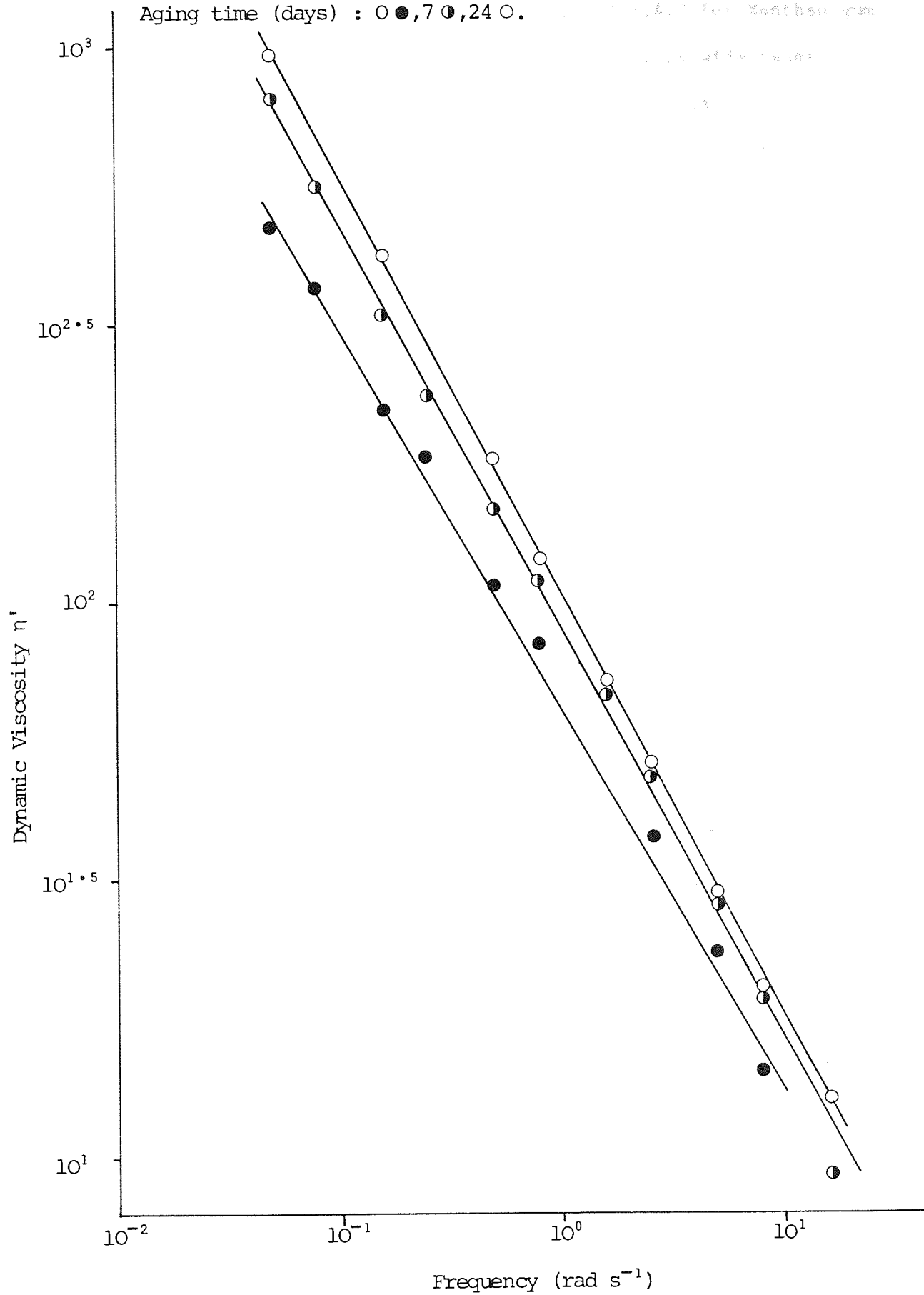
3.5 Discussion

From the results of Sections 3.4.1. and 3.4.2 for Xanthan gum and Carbopol systems, it is clear that a very wide range of rheological properties is available with the use of polyelectrolyte combinations. The range can be further extended by applying high shear to the systems. The accurate rheological measurements from oscillatory testing can then be used in conjunction with correlations with settling rate, such as that of Equation 3.4., to calculate the time for which a suspension can stand without significant sedimentation.

Application of the Cox-Merz rule (109) to collate oscillatory and continuous shear data for single and mixed polyelectrolyte systems did not yield good correlations. The absolute value of the complex viscosity, $|\eta^*|$, was calculated using Equation 3.6.

$$|\eta^*| \quad = \quad [(\eta')^2 + (\eta'')^2]^{\frac{1}{2}} \qquad 3.6$$

$|\eta^*|$ and the apparent viscosity, η_{app}, were plotted against frequency and shear rate respectively using log-log axis. An example of such a plot is shown in Figure 3.42.. The frequencies and shear rates used do not overlap, therefore direct comparisons are difficult but generally, it was found that $|\eta^*|$ decreased with ω more rapidly than η_{app} decreased with $\dot{\gamma}$ as experienced by previous workers (186,187). Hence, from the data available, it is not possible to extend the range of oscillatory results with continuous shear data.

Figure 3.42. Comparison of Dynamic and Steady Shear Viscosities; Absolute Value of Complex Viscosity, $|\eta^*|$ against Frequency, ●, and Apparent Viscosity, η_{app} against Shear Rate, ○.
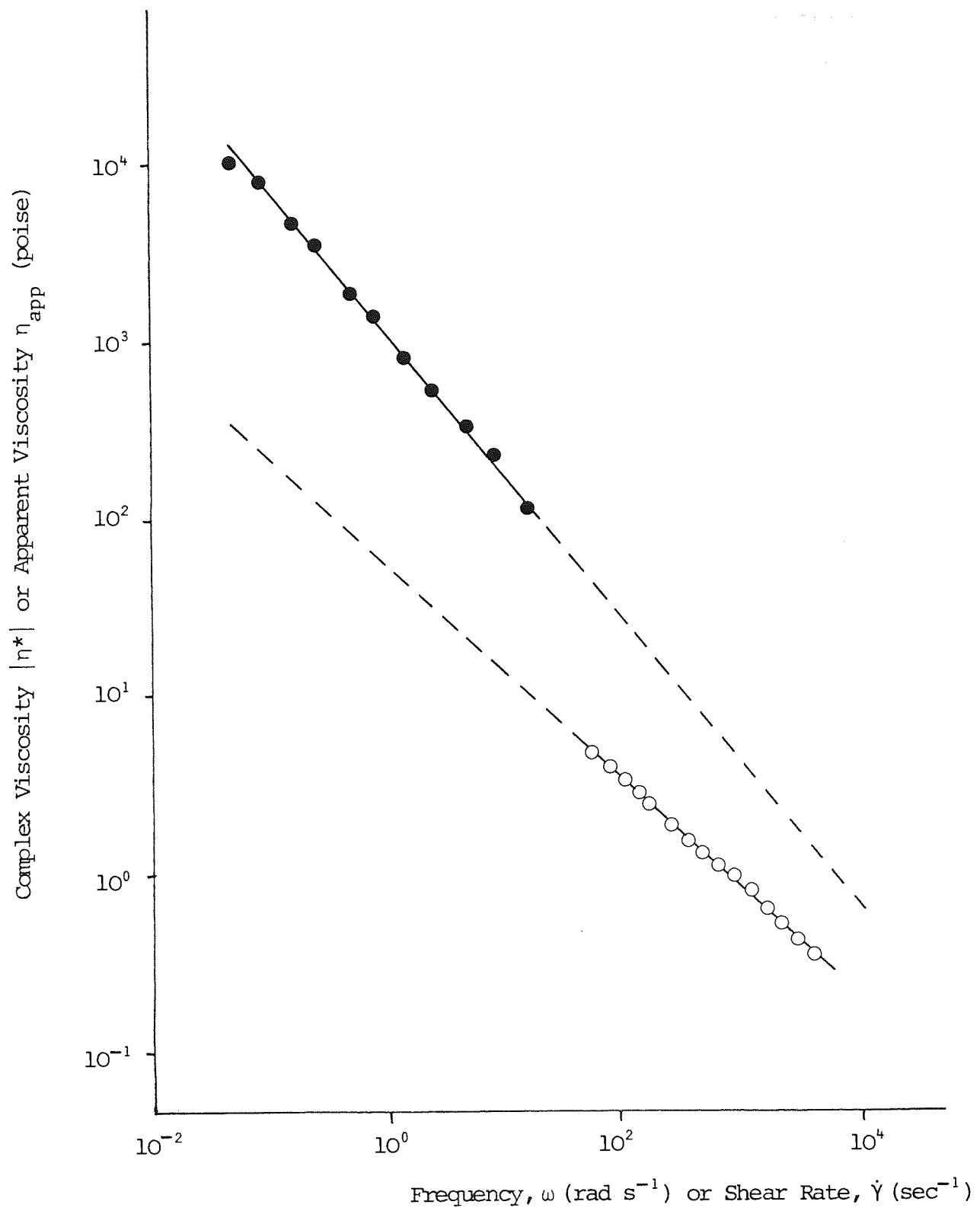
If meaningful results for viscoelastic systems can be obtained from $\tau(\dot{\gamma})$ curves, then there is little point in carrying out oscillatory tests which are more time consuming and more expensive. However, transformation of continuous shear parameters to obtain elasticities has not been demonstrated. It is also difficult to accurately determine the zero shear viscosity of many non-Newtonian materials using an instrument such as the 'Rheomat 30', even with the aid of the Cross Equation (see Table 2.3). Despite the curve-fitting of continuous shear rheograms to semi-empirical equations such as the Shangraw Equation, more useful rheological information is obtained from more elaborate techniques.

From the data presented here, it is clear that a very wide range of rheological 'profiles' are available when different polyelectrolytes are combined in solution. Close monitoring of the rheological parameters in terms of the viscous and elastic components is possible using oscillatory shear testing. Fundamental data such as this should be capable of correlation with some other formulation factor, for example, sedimentation rate of solid in liquid dispersions.

4.   NUMERICAL ANALYSIS OF APPROXIMATIONS TO DIFFUSION RATE
     EQUATIONS.

4.1 Introduction

The diffusion process is applicable to many areas of
pharmaceutics research. One of the most studied applications
is the release of drugs from polymer devices (188-191) whereby
the polymer properties are chosen such that diffusion becomes
the rate-determining step for drug release. However, whilst
it is scientifically pleasing to be able to design a dosage
form such that the drug is released at a predicted rate, it is
frequently the case that diffusion is the rate-determining
step by default, not by design.

An example of this is reflected in the work of Barzegar-Jalali
and Richards (192,193) who showed a rank order correlation
between kinetic parameters describing the in vitro and in vivo
release of Aspirin with the viscosity of the suspension
medium. The most likely link between drug release and
viscosity in this case, is diffusion of the drug through the
viscous medium; the drug solubility is unlikely to be
drastically affected by low concentrations of suspending
agents. In effect, the thickness of the boundary layer around
the dissolving drug particles is greater in more viscous
media.

That Barzegar-Jalali and Richards were only able to describe
a rank order correlation was probably in the first place a
deficiency of the experimental method. Tyrrell (194) has

explained the practical difficulties involved in studying

diffusion in viscous media caused by the large time scale

during which measurements need to be taken. In the second

place, Barzegar-Jalali and Richards' measurements of viscosity

by continuous shear methods probably contributed to the

inconclusive results. It can be hypothesised that accurate

measurement of diffusion coefficients and viscoelastic

parameters for the drug in solutions of suspending agents

would lead to a quantitative relationship.

For quantitative interpretation of experimental data from

diffusion experiments, it is necessary to use the appropriate

equation to describe the mass transfer. If the diffusion can

be described by steady state kinetics, then solutions to

Fick's First Law, Equation 4.1. are used; if unsteady state

conditions prevail, then solutions to Fick's Second Law,

Equation 4.2. are applied.

$$F \quad = \quad -D \ \frac{\partial C}{\partial x} \qquad\qquad \text{———— 4.1}$$

$$\frac{\partial C}{\partial t} \quad = \quad D \ \frac{\partial^2 C}{\partial x^2} \qquad\qquad \text{———— 4.2}$$

The terms in all Equations are defined in the Appendix to

this chapter. These Equations were derived by Fick in 1855

(195) who developed the analogy of diffusion with heat

conduction, the theories for which were developed by Fourier

in 1822 (196).

Solutions to Fick's Second Law can take many different forms

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depending upon the geometry and behaviour of the diffusion system under study. Many examples are dealt with by Crank (197) and Barrer (198); many of the equations are derived exhaustively in the treatise on heat conduction by Carslaw and Jaeger (199). It should be noted that systems exist which do not obey Fick's Laws (200).

In diffusion problems of pharmaceutical interest, the systems described by Higuchi (201,202) are widely applicable. These are based on the planar diffusion solution to Fick's Second Law:

$$Q = hC_O \left[1 - \frac{8}{\pi^2} \sum_{n=o}^{\infty} \frac{1}{(2n+1)^2} \exp\left(\frac{-D(2n+1)^2 \pi^2 t}{4h^2}\right) \right]$$

$$\text{———— 4.3.}$$

when applied to a system such as that described in Figure 4.1. With regard to Figure 4.1., we are interested in a donor phase of thickness h. The model is based on a profile of thickness $\ell = $ 2h reflected about x = o and superposed upon o < x < h. Therefore, the effective thickness for the purpose of the solution is 2h.

Figure 4.1. Scheme for the Planar Diffusion of
a drug from a Donor Phase Matrix to a Sink.

Boundary Conditions

$C = C_0$ $0 < x < h$ $t = 0$

$C = 0$ $x = 0$ $t > 0$

$C = 0$ $x \geqslant h$ $t \geqslant 0$
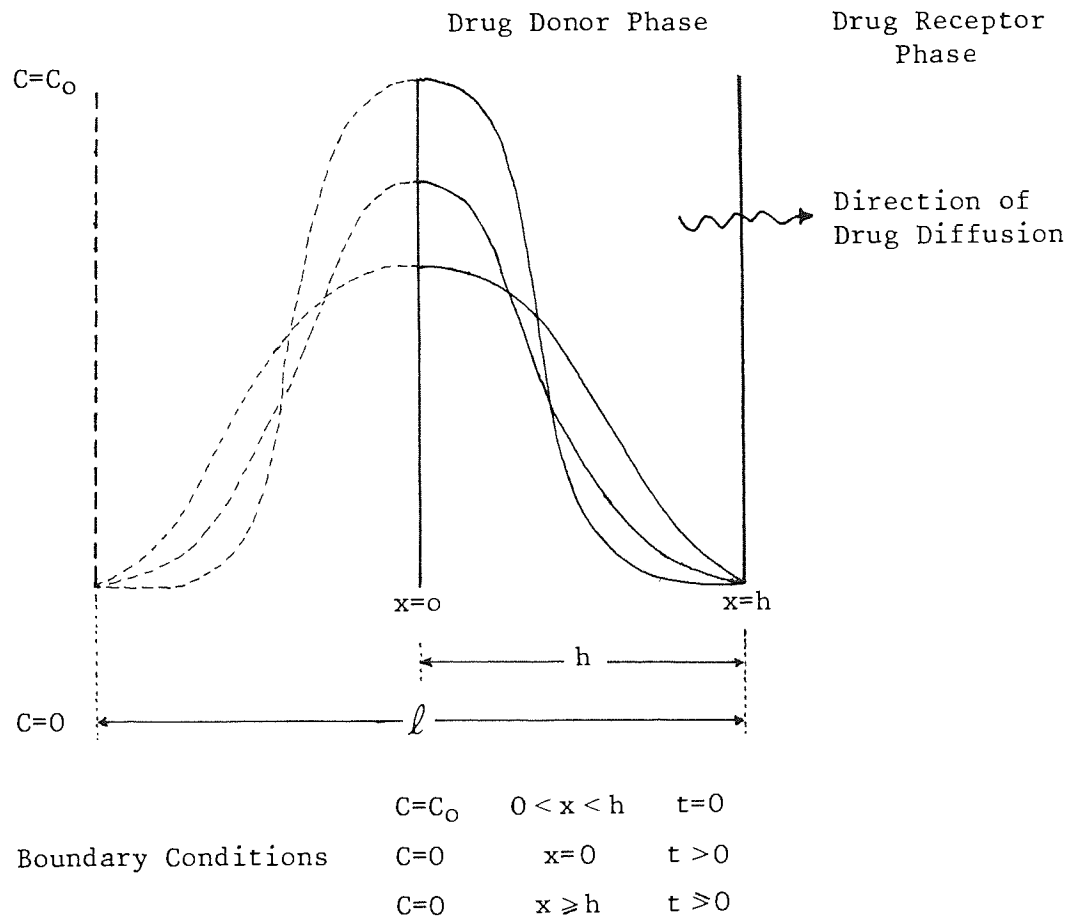
Higuchi (201) stated: "it can be easily shown that" the

Equation:

$$Q = 2C_O \sqrt{\frac{Dt}{\pi}} \qquad\qquad 4.4.$$

is a useful short time approximation for Equation 4.3. "for up

to about 30 - 50% drug release" (202). Ostrenga et

al (203) wrongly stated that Equation 4.4. is obtained by

considering the first term in the sum of Equation 4.3..

Hadgraft (204) recognised that Equation 4.4. is actually

derived from an alternative solution to Fick's Second Law:

$$Q = hC_O \left[2 \sqrt{\frac{Dt}{h^2}} \left(\frac{1}{\sqrt{\pi}} + 2 \sum_{n=1}^{\infty} (-1)^n \text{ ierfc } \frac{nh}{2\sqrt{Dt}} \right) \right] \qquad 4.5.$$

At short times, the second term of the inner brackets

disappears, thus leaving Equation 4.4.. Ierfc is the integral

error function, a standard function for which tabulated values

are available (205,206) although it can be evaluated from the

equation:

$$\text{ierfc } (x) = \frac{1}{\sqrt{\pi}} \exp^{-x^2} - x \text{ erfc } (x) \qquad 4.6.$$

$$\text{where} \quad \text{erfc } (x) = 1 - \text{erf } (x) \qquad 4.7.$$

$$\text{and the error function erf } (x) = \frac{2}{\sqrt{\pi}} \int_O^x \exp^{-z^2} dz \qquad 4.8.$$

Equation 4.3. is useful for its rapid convergence at long

times where only the first term in the exponential series

is significant and we obtain:

$$Q = hC_O \left[1 - \frac{8}{\pi^2} \exp \left(- \frac{Dx^2 t}{4h^2} \right) \right] \quad\text{——— 4.9.}$$

The use of approximations to the diffusion rate equations has been studied by Hadgraft and Guy (204,207) who have shown graphically the difference between the "square-root-time approximation", Equation 4.4., and the rigorous solution. As a further development of this theme, the intention of the work presented here is to rigorously quantify the errors involved in using either the short or long time approximations. An accurate knowledge of the inherent errors of these equations should provide a basis for obtaining quantitative correlations with, for example, viscoelastic parameters of non-Newtonian diffusion media.

Certain studies on drug release from creams and ointments, for example by Ostrenga et al (203) and Chowhan and Pritchard (208) show data analysis in terms of Equation 4.4. with good agreement. However, from the numerical method used in the present study, it can be shown that analysis of drug release profiles alone does not provide unambiguous information about the mechanism of rate control. In other words, for experimental systems concerning such complex materials as creams and ointments, it is necessary to obtain further evidence for rate controlling diffusion before Equation 4.4. can be applied.

4.2 Derivation of a Diffusion Rate Equation

Equation 4.3. and 4.5. are solutions to Fick's second Law
obtained by different methods. The former can be obtained
by the method of Separation of Variables; the latter by
Reflection and Superposition and both equations can be
obtained by Laplace transformation (197,198). Equation 4.3.
has been widely used in the pharmaceutical and allied
literature (202,209) and its derivation from Equation 4.2.
as the most straightforward.

The method of Separation of Variables is a standard solution
method for partial differential equations (210). In this
case, we assume that Equation 4.2. can be solved by an
equation of the form:

$$C\,(x,\,t) \quad = \quad X\,(x).\,T\,(t) \qquad\qquad 4.10.$$

where X is a function of x only and T a function of t only.
If we consider the partial differential Equations 4.11 and
4.12.:-

$$\frac{\partial C}{\partial t} \quad = \quad X\,\frac{dT}{dt} \qquad\qquad 4.11.$$

$$\frac{\partial^2 C}{\partial x^2} \quad = \quad T\,\frac{\partial^2 X}{\partial x^2} \qquad\qquad 4.12.$$

then from Equation 4.2. we obtain Equation 4.13.:

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$$\frac{1}{DT} \frac{dT}{dt} = \frac{1}{X} \frac{d^2 X}{dx^2} \qquad\qquad 4.13.$$

Here, the left hand side is dependent on t only and the right hand side only on x. The next stage involves setting each side of Equation 4.13 equal to a constant, $-\lambda^2$, where λ is a real number and the negative sign ensures an exponentially decreasing solution in t.

Considering the left hand side of Equation 4.13. we obtain

$$\frac{dT}{T} = -\lambda^2 Ddt \qquad\qquad 4.14.$$

which on integration gives:

$$T = E \exp(-\lambda^2 Dt) \qquad\qquad 4.15.$$

where E is the integration constant.

The solution to the right hand side of Equation 4.13. is given by

$$X = A \, Sin\lambda x + B \, Cos\lambda x \qquad\qquad 4.16.$$

with A and B as integration constants. Substitution into Equation 4.10. gives:

$$C(x, t) = (A' \, Sin\lambda x + B' \, Cos\lambda x) \, e^{-\lambda^2 Dt} \qquad 4.17.$$

where A' = AE and B' = BE. Substituting the relevant boundary conditions:

$$C(0, t) = B' e^{-\lambda^2 Dt} = 0 \qquad\qquad 4.18.$$

therefore $B' = 0$ for all values of t. This leads to the result:

$$C(\ell, t) = A' \operatorname{Sin} \lambda\ell \ e^{-\lambda^2 Dt} = 0 \qquad 4.19.$$

which gives non-trivial solutions of C for $\operatorname{Sin} \lambda\ell = 0$,

i.e. $\lambda = n\pi/\ell$ where n = 1,2,3......... For convenience,

$\ell = 2h$, see Figure 4.1. Substituting $B' = 0$ and $\lambda = n\pi/\ell$

into Equation 4.17. gives:

$$C(x, t) = \sum_{n=1}^{\infty} A_n' \ \operatorname{Sin}\left(\frac{n\pi x}{\ell}\right) \exp\left(\frac{-n^2\pi^2 Dt}{\ell^2}\right) \qquad 4.20.$$

where A_n' is a constant such that at $t = 0$,

$$C(x, 0) = C_0 = \sum_{n=1}^{\infty} A_n' \ \operatorname{Sin}\left(\frac{n\pi x}{\ell}\right) \qquad 4.21$$

The next stage, the evaluation of A_n', involves the use of a Fourier series which is defined by an equation of the form: (211)

$$f(x) = \frac{a_0}{2} + \sum_{r=1}^{\infty} a_r \operatorname{Cos} \ rx + b_r \operatorname{Sin} rx \qquad 4.22.$$

The shape of the concentration profile within the drug donor phase is sinusoidal, similar to $-\pi/2 < x < \pi/2$. In this region, $\operatorname{Sin}(x)$ is an odd function; an odd function occurs when $f(x) = -f(-x)$ ie, it is not symmetrical about the

y-axis. If $f(x)$ in Equation 4.22. is odd then we obtain

$$f(x) = \sum_{r=1}^{\infty} b_r \; Sin \; rx \qquad\qquad 4.23.$$

because the Cosine term becomes zero on integration and consideration of $a_o/2$ is not necessary. It is now seen that A_n' is equivalent to b_r . The infinite series can be simplified using Dirichlet's condition (212) for a periodic function that $f(x) = f(x + 2k\pi)$ where k is any integer. Thereby,

$$b_r = \frac{2}{\pi/2} \int_{\pi/2}^{\pi} f(x) \; Sin \; rx \; dx \qquad\qquad 4.24.$$

from a consideration of the shape of the concentration profile compared to the Sine wave in the region of interest. From Equations 4.21. and 4.24., A_n' can be evaluated:

$$A_n' = \frac{2}{\ell} \int_{o}^{\ell} C_o \; Sin \left(\frac{n\pi x}{\ell} \right) dx \qquad\qquad 4.25.$$

On integration, we obtain

$$A_n' = \frac{2C_o}{\ell} \cdot \frac{\ell}{n\pi} \left\{ - Cos \left(\frac{n\pi x}{\ell} \right) \right\}_{o}^{\ell} \qquad\qquad 4.26$$

$$A_n' = \frac{4C_o}{n\pi} \qquad for \; n = 1,3,5..... \qquad 4.27$$

Substituting into Equation 4.20.:

$$C = C(x,t) = \sum_{n=o}^{\infty} \frac{4C_o}{(2n+1)\pi} \; exp\left(- \frac{D(2n+1)^2 \pi^2 t}{\ell^2} \right) Sin \left(\frac{(2n+1)\pi x}{\ell} \right)$$

$$4.28$$

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Integration of Equation 4.28. between the limits 0 and ℓ will provide Q, the cumulative amount of drug released from the matrix. On integration, the Sine term becomes a Cosine term such that Cos (y) = + 1 when $x = \ell$ and Cos (y) = - 1 when x = 0, where $y = (2n + 1)\pi x / \ell$. Therefore the trigonometrical term disappears and we are left with:

$$Q = hC_o \left\{ 1 - \frac{8}{\pi^2} \sum_{n=o}^{\infty} \frac{1}{(2n + 1)^2} \exp \left(- \frac{D(2n+1)^2 \pi^2 t}{4h^2} \right) \right\}$$

4.29.

where $Q + Q_r = hC_o$, Q_r being the quantity of drug remaining in the donor phase matrix. This is identical to Equation 4.3..

4.3 Method of Numerical Analysis

In order to assess the limits of applicability of the approximate Equations 4.4. and 4.9. compared to the rigorous expressions, it is necessary to employ a variable term that is common to all of the Equations. First of all, since Equations 4.3. and 4.5. are for all practical purposes equivalent, only Equation 4.3. will be considered in the numerical analysis; accurate comparison of these two equations using a double precision Fortran IV computer programme of the type described below revealed discrepancies only in the eighth decimal place for the fraction of drug released at time, t.

By dividing Equations 4.4., 4.3, and 4.9. by hC_o, the left hand sides become the dimensionless ratio Q/hC_o representing

the fraction, F, of drug released from the matrix at time, t.

Hence,

$$\frac{Q_1}{hC_o} = F_1 = 2 \left\{ \frac{Dt}{h^2 \pi} \right\}^{\frac{1}{2}} \qquad\qquad 4.30.$$

$$\frac{Q_2}{hC_o} = F_2 = \left\{ 1 - \frac{8}{\pi^2} \sum_{n=o}^{\infty} \frac{1}{(2n+1)^2} \exp\left(-\frac{D(2n+1)^2 \pi^2 t}{4h^2} \right) \right\}$$

$$\qquad\qquad 4.31.$$

$$\frac{Q_3}{HC_o} = F_3 = \left\{ 1 - \frac{8}{\pi^2} \exp\left(-\frac{D\pi^2 t}{4h^2} \right) \right\} \qquad 4.32.$$

It is noticeable that all three expressions contain the term Dt/h^2 and that this term is dimensionless with reference to Equation 4.30.. Crank (197) has made extensive use of the Dt/h^2 term. By substituting χ for $(\pi^2 Dt/4h^2)^{\frac{1}{2}}$ in Equations 4.30. to 4.32. we obtain:

$$F_1 = \frac{4\chi}{\pi^{3/2}} \qquad\qquad 4.33.$$

$$F_2 = \left\{ 1 - \frac{8}{\pi^2} \sum_{n=o}^{\infty} \frac{1}{(2n+1)^2} \exp\left(-(2n+1)^2 \chi^2 \right) \right\} \qquad 4.34.$$

$$F_3 = \left\{ 1 - \frac{8}{\pi^2} \exp\left(-\chi^2 \right) \right\} \qquad 4.35$$

The approximation of interest is now $F_1 \simeq F_2 \simeq F_3$. By inserting suitable values for χ into Equations 4.33. to 4.35., the fractions released according to Equations 4.4.,

4.3. and 4.9. respectively, were obtained. To ensure that the calculated differences between F_1, F_2 and F_3 were due to the respective equations and not to the method of calculation, a double precision Fortran IV Computer programme was used. The algorithm for this programme is given in Figure 4.2. and the corresponding listing is given in Table 4.1.. The exponential series in Equation 4.34. was evaluated such that the sum of the last ten terms was less than 10^{-10}. This guaranteed that the series had converged.

Figure 4.2. Algorithm for Determination of the Fractions Released, F_1, F_2 and F_3 according to the Three Diffusion Equations.

START

Variable χ, ie, $x = 0.0$
χ increment, INT $= 0.05$

$x = x + INT$

IS $x > 2.5$?

YES → STOP

NO

Summation Index $N = 0$
TERM (I), I = 1,200 = 0.0
where TERM =
$$\frac{1}{(2N+1)^2} \exp -(2N+1)^2 x^2$$

Evaluate F_1 and F_2

Evaluate TERM (N+1)

SUM = SUM + TERM (N+1)

Evaluate F_2

Evaluate E_1 and E_3, the % errors in F_1 and F_3 relative to F_2

IS $N > 11$?

YES → Evaluate TSUM, the sum of the last 10 values of TERM

NO → N = N + 1

IS (TSUM − SUM) $> 10^{-10}$?

No → N = N + 1

Yes → Write x, F_1, F_2, F_3, E_1, E_3.

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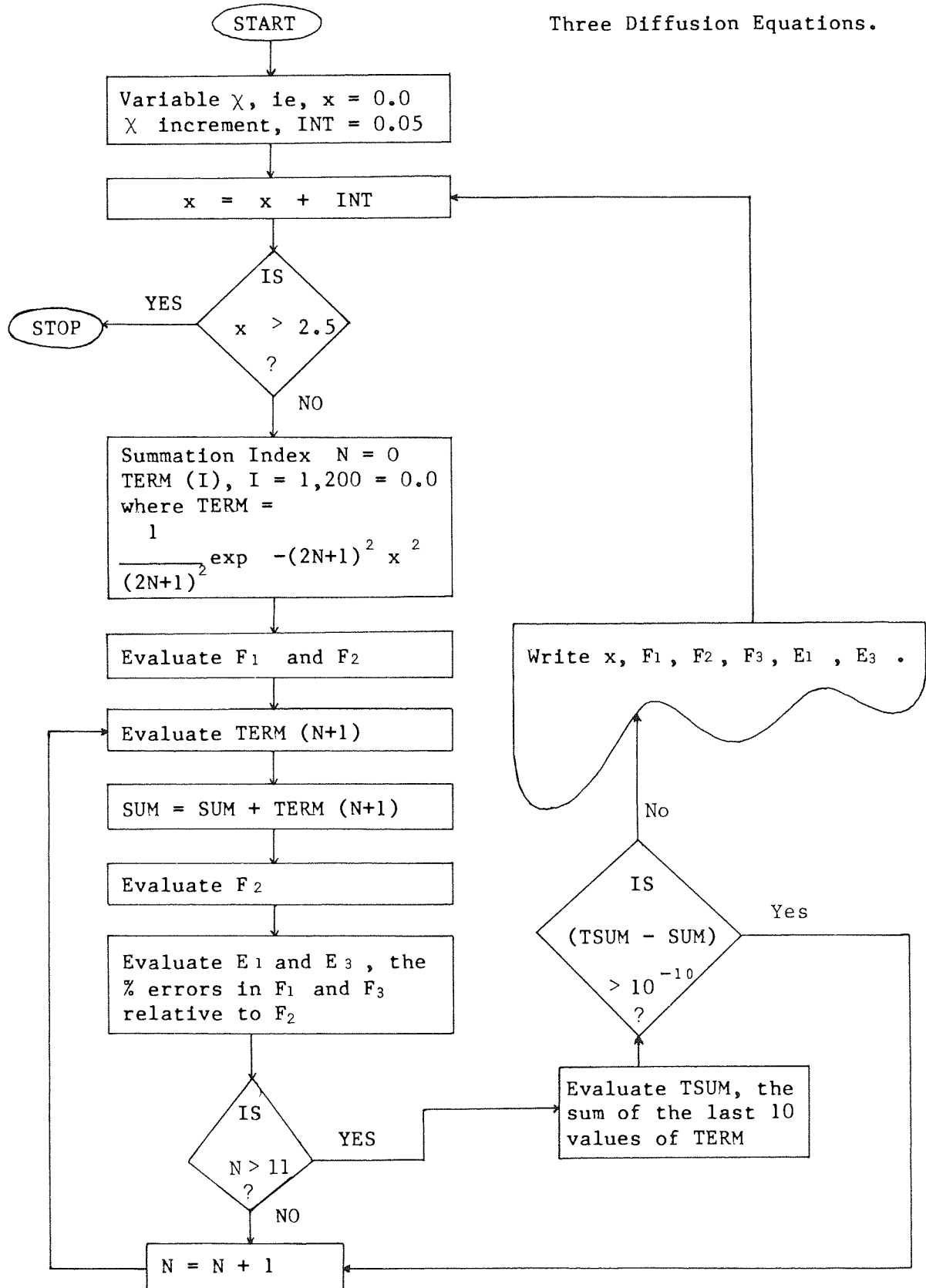
Table 4.1. Listing of the Double Precision Fortran IV Programme
           for Calculating the Fractions Released F_1 , F_2 , F_3
           according to the Three Diffusion Equations.

```
       MASTER SEGMENT
       REAL INT
       DOUBLE PRECISION PI, F1, F2, F3, E1, E3, D, Y
      1                    TERM, SUM, TSUM
       DIMENSION TERM (200)
       X = 0.0
       INT = 0.05
   1   X = X + INT
       IF (X.GT.2.5) GOTO 7
       M = 0
       DO 6  I = 1,200
       TERM (I) = 0.0
   6   CONTINUE
       SUM = 0.0
       PI = 3.141592653589793238462643
C      EVALUATE F1:
       F1 = (4.0 * DBLE(X)/(PI * SQRT(PI)))
C      EVALUATE F2:
   2   D = DBLE ((2.0 + FLOAT(N) + 1.0) **2)
       Y = EXP (-D * DBLE (X **2))
       TERM (N+1) = Y/D
       SUM = SUM + TERM (N+1)
       F2 = (1.0 - ((8.0/(PI**2))*SUM))
       E1 = 100.0 * ((F1-F2)/F2)
       IF (N.GT.11) GOTO 4
   5   N = N + 1
       GOTO 2
   4   TSUM = 0.0
       DO 20 J = N - 10,N
       TSUM = TSUM + TERM(J)
  20   CONTINUE
       TSUM = TSUM + SUM
       IF (ABS(TSUM - SUM). GE.1.0.D-10) GOTO 5
C      EVALUATE F3:
       F3 = 1.0 - (8.0/(PI**2)*TERM(1))
       E3 = 100.0*((F3-F2)/F2)
       WRITE(6,23)X,F1,F2,F3,E1,E3
  23   FORMAT (1X,F5.2,5(1X,D25.20))
       GOTO 1
   7   STOP
       END
       FINISH
* * * *
```

The percentage errors involved in using either approximate

equation at any stage of an experiment were quantified by E_1

and E_3 where

$$E_1 = 100 \left(\frac{F_1 - F_2}{F_2} \right) \qquad 4.36$$

$$E_3 = 100 \left(\frac{F_3 - F_2}{F_2} \right) \qquad 4.37$$

4.4 Results and Discussion

The abridged results of the computation described above are

listed in Table 4.2. showing the errors involved in using

either approximation Equation 4.4 or 4.9. relative to the

'exact' fraction released, F_2 . To avoid the use of Equation

4.3., it is clearly justified to apply Equation 4.4. for less

than 50% release or a first order plot according to Equation

4.9. for greater than 50% release. No more than about 0.2%

error is thus incurred in values of F. This is illustrated

in Figure 4.3. where F_1 , F_2 , and F_3 are plotted against

χ^2 , which is proportional to time.

If data for the true fraction released, F_2 , is plotted in

a first order fashion against χ^2, then

linear least mean square regression analysis in the range

$0.07 < F < 0.97$ gave correlation coefficients in excess of

0.999 (N=11).

Table 4.2. Results of Numerical Analaysis using the Programme
            listed in Table 4.1.

χ	F_1	F_2	F_3	E_1	E_3
0.1	0.07184	0.07184	0.19750	$< 10^{-6}$	174.95
0.2	0.14367	0.14364	0.22121		53.974
0.3	0.21550	0.21550	0.25920		20.274
0.4	0.28734	0.28734	0.30928	1.1941×10^{-6}	7.6352
0.5	0.35917	0.35917	0.36873	4.5958×10^{-4}	2.6604
0.6	0.43101	0.43095	0.43448	0.012867	0.81940
0.7	0.50284	0.50233	0.50342	0.10254	0.21796
0.8	0.57468	0.57231	0.57259	0.41407	0.049500
0.9	0.64651	0.63935	0.63941	1.1204	9.6117×10^{-3}
1.0	0.71835	0.70180	0.70181	2.3584	1.5837×10^{-3}
1.1	0.79018	0.75829	0.75829	4.2061	2.2143×10^{-4}
1.2	0.86202	0.80795	0.80795	6.6916	2.6167×10^{-5}
1.3	0.93385	0.85043	0.85043	9.8090	2.6330×10^{-6}
1.4	1.00569	0.88582	0.88582	13.531	
1.5	1.07752	0.91457	0.91457	17.818	
1.6	1.14936	0.93734	0.93734	22.619	
1.7	1.22119	0.95495	0.95495	27.880	$< 10^{-6}$
1.8	1.29303	0.96825	0.96825	33.942	
1.9	1.36486	0.97807	0.97807	39.546	
2.0	1.43669	0.98515	0.98515	48.835	
2.1	1.50853	0.99015	0.99015	52.354	
2.2	1.58037	0.99359	0.99359	59.056	
2.3	1.65220	0.99591	0.99591	65.898	
2.4	1.72404	0.99745	0.99745	72.845	

Figure 4.3. The Fraction F of Drug Released by Planar Diffusion to a Perfect Sink. F_1 ········ Short time approximation; F_2 ——— Rigorous solution; F_3 —··— long time approximation.

$$\chi^2 = \frac{\pi^2 \, Dt}{4h^2}$$

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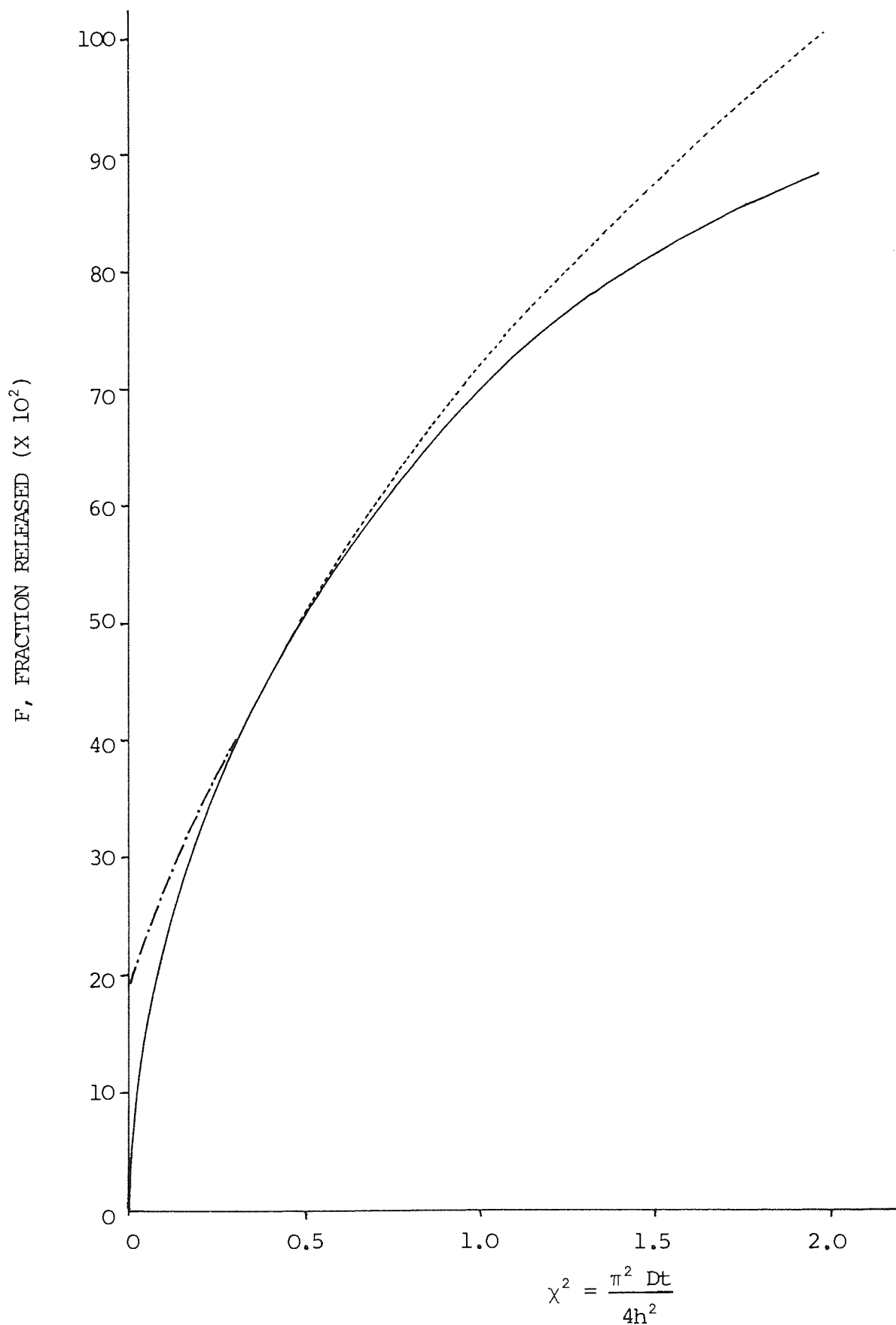
This result is illustrated in Figure 4.4. and the data used is given in Table 4.3.. It is important when considered in the light of a set of experimental drug release data where the mechanism of rate control has not been firmly established as diffusion. Clearly, if data from a wholly diffusion controlled process, as is the case for F_2 , can provide a good fit to first order behaviour, then it must be difficult, within experimental error, to distinguish the mechanism of rate control merely from analysis of drug release profiles.

Figure 4.4. First Order Plot of the Actual Fraction, F_2, of Drug Released by Planar Diffusion into a Perfect Sink.

$$\chi^2 = \frac{\pi^2 \ Dt}{4h^2}$$
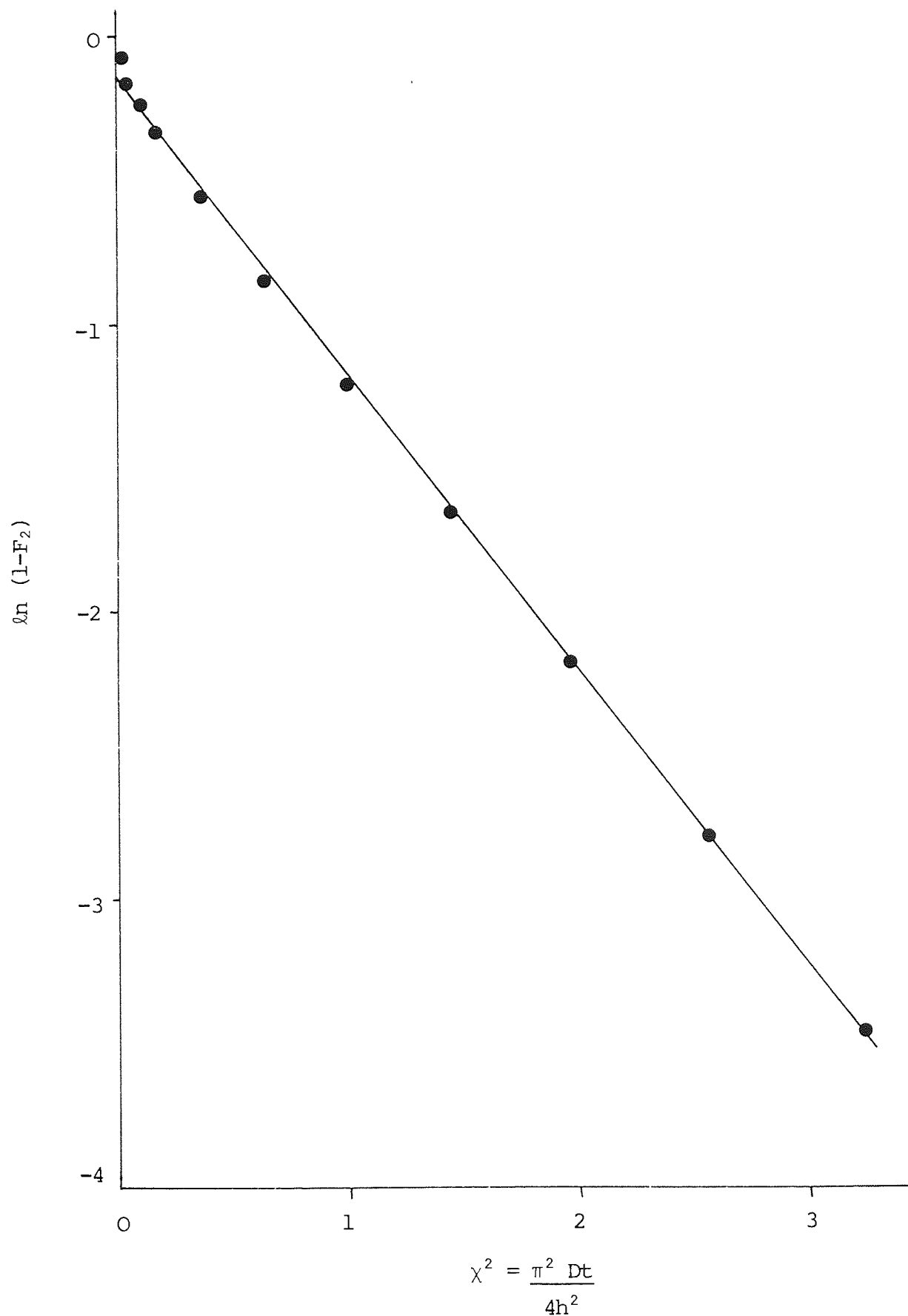
Table 4.3. Diffusional Data used for the First Order Plot of Figure 4.4.

χ^2	F_2	$\ln(1-F_2)$
0.01	0.07184	−0.075
0.04	0.14364	−0.155
0.09	0.21550	−0.243
0.16	0.28734	−0.339
0.36	0.43095	−0.564
0.64	0.57231	−0.849
1.00	0.70180	−1.210
1.44	0.80795	−1.650
1.96	0.88582	−2.170
2.56	0.93734	−2.770
3.24	0.96825	−3.450

Appendix I. Glossary of Terms not Directly Explained in the Text.

Term	Equation of first appearance	Meaning	Units
a_o, a_r, b_r	4.22.	Constant terms in Fourier Series	
C	4.1.	Concentration	ML^{-3}
C	4.4.	Initial Concentration in donor phase matrix.	ML^{-3}
dC/dx	4.1.	Concentration gradient	ML^{-4}
D	4.1.	Diffusion Coefficient	$L^2 T^{-1}$
E	4.36.	% error incurred from Eqn.4.4.	
E	4.37.	" " " " " 4.9.	
F	4.30.	Fraction released according to Eqn.4.4.	
F	4.31.	Fraction released according to Eqn.4.3.	
F	4.32.	Fraction released according to Eqn.4.9.	
F	4.1.	Flux: amount released per unit area per unit time.	$ML^{-2} T^{-1}$
h	4.3.	Thickness of donor phase matrix	L
ℓ	4.19.	Hypothetical thickness of donor phase matrix	L
n	4.3.	Summation Index	
Q	4.3.	Amount released per unit area at time, t.	ML^{-2}
Q_1	4.30.	Release rate according to Eqn. 4.4.	ML^{-2}
Q_2	4.31.	Release rate according to Eqn. 4.3.	ML^{-2}
Q_3	4.32.	Release rate according to Eqn. 4.9.	ML^{-2}

r	4.22.	Summation index for Fourier Series	
t	4.2.	Time	T
x	4.1.	Distance	L
z	4.8.	Arbitrary variable	
χ	4.33.	Dimensionless variable = $(\pi^2 \, Dt/4h^2)^{\frac{1}{2}}$	

M = Mass,   L = Length and T = Time.

5. DIFFUSIONAL AND RHEOLOGICAL PROPERTIES OF ALGINATE GELS.

5.1 Introduction

This chapter is concerned with the relationship of dynamic rheological properties of Alginate cross-linked by means of Calcium, Ca^{2+} ions, with the diffusion of a drug, Ibuprofen, in the gel matrix.

As discussed in Section 1.2, Alginate forms rigid gels with with all divalent metal ions except magnesium. This characteristic has found wide application in the food industry (104, 105) as well as the pharmaceutical uses explained in Section 1. In Section 2, the problems of determining the molecular properties of a biological material were considered: this yielded detailed information about the particular Alginate used in this study. Section 3 was concerned with the wide variety of rheological properties available in Alginate systems when combined with other polyelectrolytes. The dynamic rheological data obtained by oscillatory shear testing provided fundamental parameters describing the flow properties.

In this Section, the diffusional aspects of Calcium Alginate gels are investigated. The results of the numerical analysis of diffusion equations in Section 4. are borne in mind for the interpretation of drug release data. By way of comparison with diffusional characteristics, the mechanical properties of the gels are examined using oscillatory shear tests.

Such rheological testing is particularly convenient for the brittle Calcium Alginate gels encountered: small amplitude oscillatory shear between parallel plates means that the net deformation of the sample is negligible and the material is effectively unchanged during testing. Continuous shear testing would not be feasible in this case because sample slippage and fracture would occur. Also, locating an intact Calcium Alginate gel in any continuous shear geometry would be manipulatively difficult.

The diffusion of solutes through viscous and gel-like media is of wide academic and industrial interest. In the pharmaceutical field, much interest has been centred on hydrogels and their use as controlled release drug delivery systems (213-215), and the study of diffusion is widespread in the formulation of ointments and creams (203, 208, 216, 217) and suppositories (218). Most systems of pharmaceutical interest involve the diffusion of a drug through a viscous and often non-Newtonian medium. Hence, we are faced with two problems. Firstly, as Tyrrell pointed out, (194), even with modern experimental methods, the determination of diffusion coefficients with reasonable precision is difficult, especially in viscous media. Although it is often assumed that diffusion coefficients are inversely proportional to the shear viscosity, this is the exception rather than the rule. It has been shown that the product of diffusion and viscosity coefficients, $D\eta$, increases with the viscosity of the

continuous phase (219, 220). Secondly, to get an insight into the diffusion-rheology relationships, rheological measurements should represent the physical equilibrium rest state of the material as exists for diffusion experiments. The second problem can be largely overcome with the use of established rheological techniques.

There have been very few studies, especially in the pharmaceutical literature that have attempted to link the diffusion of a solute through a gel or viscous phase with dynamic rheological data. A recent example of such a study is that of Sherriff and Enever (221). The diffusion of Methyl Salicylate was monitored as a function of the Storage Modulus G' (ω) of oil gels prepared by dispersing colloidal silica in n-dodecane and 1-dodecanól. For the 1-dodcanol system, the drug release rate was inversely proportional to G'. Even so, the authors considered only the elastic and not the viscous components of the dynamic rheological data. From a consideration of the Stokes-Einstein relationship that the product $D\eta/T$ should be constant for a given solute, one would expect that the viscous component would most likely dominate the effect on the diffusion coefficient. However, it has not been firmly established whether or not the elastic component makes a significant contribution, albeit smaller than the viscous component.

Previous studies have shown conflicting evidence as to the effect on the diffusion coefficient of low concentrations

of gelling agents or polymers in solution. Most of the published work has involved widely differing materials and this makes absolute comparisons difficult. The material most regularly studied is gelatin. Friedman and Kramer (222, 223) found that the diffusion of sucrose and urea increased by about 40% when the gelatin concentration was decreased from 4 to 12%. Nixon and co-workers (224) showed that diffusion of methylene blue dye was dependent on concentration in the range 10 to 15% gelatin in gelatin-glycerol-water gels. Taft and Malm (225) used the analogy of electrical conductivity with diffusion to show that diffusion of elemental cations was almost independent of gelatin concentration up to 13.2%, (specific conductivity decreased by only 4 to 8%). Marriott and Kellaway (218) found that the time taken for 75% release of proflavine from erodable gelatin-glycerol-water gels at $37^{o}C$ increased from 9 to 30 min in the range 2 to 14% gelatin.

Other results have varied widely according to the system studied. Shaw and Schy (226) showed that D for $^{3}H_{2}O$ was reduced by 76% in Collagen 5% gel compared with the free diffusion coefficient in water. Chen-Chow and Frank (227) found that Pluronic F127 in concentrations of 20 to 30% reduced D for lidocaine from 1.75 to 1.05 x 10^{-6} $cm^{2}sec^{-1}$. Rickard et al (228) found D for iodide ions to be unaffected by Xanthan gum concentrations of 0.01 to 1.3%. Gerasimova and Bromberg (229) showed that D for thiosulphate,

thioglycolic acid and mercaptosuccinic acid decreased in the presence of 5 to 20% gelatin, hydroxyethylcellulose, carboxymethylcellulose and polyvinylalcohol. Shul'man et al (230) found that D for ferricyanide ions decreased in aqueous carboxymethylcellulose solutions in the range 0 to 15% polymer.

Little attempt was made in any of these studies to quantitatively link diffusional with rheological properties. It appears that when diffusion is studies in depth, then rheological considerations are neglected. A study of diffusion by Farag et al (231) even claimed that solutions of polyacrylamide and polyethylene oxide up to 1% were Newtonian as 'confirmed' using a Brookfield viscometer.

In a comprehensive review of mass transport models, Flynn et al (232) suggested that the three dimensional network of a polymeric gel matrix can affect diffusion rate either by interaction and adsorption or by mechanical blocking of the diffusant. This is based on the generally accepted theory that diffusion takes place only in the fluid phase so that the microscopic viscosity and the number of polymer segments determine the diffusion rate. Hence, the bulk viscosity or gel rigidity can be affected by the degree of polymerisation or cross-linking of the polymer but the diffusion rate can remain unchanged because of a constant microscopic viscosity.

In this study, the aim is to develop a simple experimental

system whereby the diffusional and dynamic rheological properties of rigid gels can be examined. When applied to Alginate gel systems, data from the two experimental techniques can be compared.

5.2   Theory

This section deals with the theoretical aspects of the techniques used in subsequent sections. The theory of gelling has been discussed in Section 1; the theory appropriate to oscillatory rheometry was given in Section 2 and the calculation of diffusion coefficient from experimental data was discussed in Section 4.

5.2.1 Diffusion Coefficient

The simplest relationship between diffusion and viscosity is provided by the Nernst-Einstein Equation (233, 234):

$$D = \frac{RT}{f} \hspace{3cm} 5.1$$

where D = diffusion coefficient

R = universal gas constant

T = absolute temperature

f = frictional coefficient

In this relationship, diffusion is influenced by molecular energy, as reflected in R, temperature, and the resistance to molecular motion, as quantified by f. The value of f for a particle in a homogeneous fluid can be defined using the Sutherland Equation (235):

$$f \quad = \quad 6\pi\eta r \quad \frac{2\eta + r\beta}{3\eta + r\beta} \qquad\qquad 5.2$$

where r = solute radius

η = solvent viscosity

β = 'slip factor'

The 'slip factor', β, or more formally, the coefficient of sliding friction, is a measure of the tendency of solute molecules to adhere to solvent molecules. For a large diffusant, solvent molecules tend to be dragged along and therefore β is large. Hence, Equation 5.2 reduces to Stokes Law (236).

$$f_{\beta \to \infty} \quad = \quad 6\pi\eta r \qquad\qquad 5.3$$

Substitution of Equation 5.3 into 5.1. gives the Stokes-Einstein Equation.

$$D = \frac{RT}{6\pi\eta N_{AV} r} \qquad\qquad 5.4$$

where N_{AV} = Avogadro's number

This was derived for describing the diffusion of large, spherical molecules where the solvent appears to act as a continuum for the diffusant.

When β is small, there is little resistance to slip and Equation 5.2. becomes

$$f_{\beta \to o} \quad = \quad 4\pi\eta r \qquad\qquad 5.5$$

This equation is useful for the case of self-diffusion, i.e,

when solvent and diffusant molecules are approximately the same size. Often, f becomes less than $4\pi\eta r$ if solvent molecules are larger than solute molecules.

Although the above relationships apply to spherical diffusants, frictional coefficients can be calculated for ellipsoids from molecular dimensions using equations derived independently by Perrin (237) and Herzog et al (238). Hence, the frictional ratio, F, is obtained ie, the ratio of the frictional resistance of an ellipsoid to that of a sphere of equal volume.

When the diffusant molecule is small, $\beta \to 0$ and substitution of Equation 5.5 into 5.1. gives:

$$D = \frac{RT}{4\pi\eta N_{AV}} \left(\frac{4\pi N_{AV}}{3v} \right)^{1/3} = \frac{kT}{4\pi\eta} \left(\frac{4\pi N_{AV}}{3v} \right)^{1/3} \qquad 5.6$$

where v = molar volume

$k = R/N_{AV}$ = Boltzmann's constant.

The molar volume, v, is usually approximated as the partial molar volume in cm^3 mol^{-1} , which is a hydrodynamic property of the molecule. Values for the partial molar volume from elements and substituent groups are tabulated by Flynn et al (232). By substituting values for the constants for diffusion in water at $25°$ C ie, π , η , k and T, we obtain

$$D = \frac{4.92 \times 10^{-5}}{v^{1/3}} \quad cm^2 \ sec^{-1} \qquad 5.7$$

By a similar treatment of Equation 5.4. and assuming a
spherical molecule so that F = 1, then the diffusion
coefficient in water at 25° C is given by

$$D = \frac{3.28 \times 10^{-5}}{V^{1/3}} \quad cm^2 \ sec^{-1} \qquad 5.8$$

5.2.2 Partition Coefficient

The experimental system employed to obtain diffusion
coefficients in Calcium Alginate gels utilised the transfer
of Ibuprofen from an aqueous gel phase to n-octanol. In such
a system, the partitioning behaviour of the solute is
important in determining the rate-controlling mechanism for
drug transfer.

It is well known that the apparent partition coefficient of
weakly ionised compounds such as Ibuprofen, varies with pH and
ionic strength. However, with a knowledge of the absolute
partition coefficient, P_u, of the unionised species between
aqueous and organic phases, the apparent partition
coefficient, P_{app}, at any particular pH can be calculated.
Irwin and Li Wan Po (239) suggested that the partition
coefficient of the ionised species, P_i, should also be
considered when lower alcohols are used in the partitioning
systems. These authors went on to derive a relationship for
obtaining P_u and P_i from data of pH, P_{app} and dissociation
constant, K_a . The derivation for a weak acid follows
similar steps to the original derivation for a weak base
(239).

If we consider the scheme given in Figure 5.1., we can

obtain expressions for P_u , P_i and P_{app}.

Figure 5.1   Partitioning of a Weak Acid
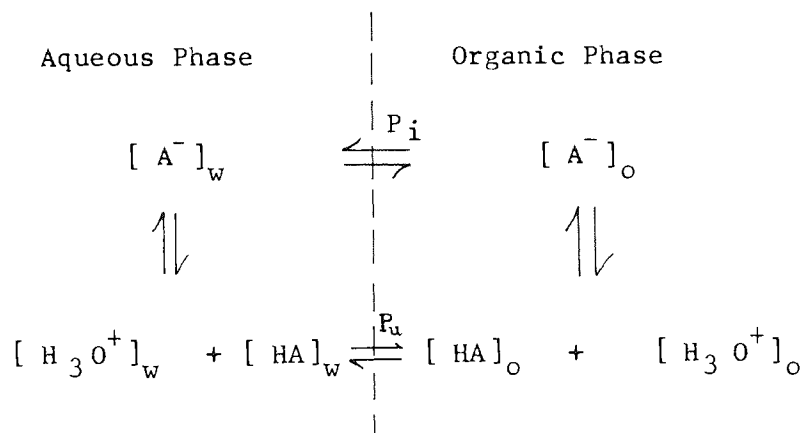
Subscripts o and w represent the organic and water

phases respectively. The dissociation of a weakly acidic

compound can be represented by.

$$HA + H_2O \rightleftharpoons A^- + H_3O^+ \qquad\qquad 5.9$$
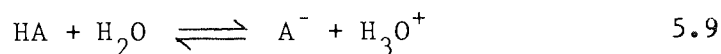
and

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \qquad\qquad 5.10$$

then

$$P_u = \frac{[HA]_o}{[HA]_w} \quad \text{and } P_i = \frac{[A^-]_o}{[A^-]_w} \qquad 5.11, \; 5.12.$$

Therefore $$P_{app} = \frac{[A^-]_o + [HA]_o}{[A^-]_w \quad [HA]_w} \qquad\qquad 5.13$$

Substituting Equations 5.13. and 5.14. in the numerator of

5.15., we obtain:

$$P_{app} = \frac{P_i[A^-]_w + P_u[HA]_w}{[A^-]_w + [HA]_w} \qquad\qquad 5.14$$

Substitution of $[A^-]w$ from Equation 5.12., cancellation of the common factor $[HA]w$ and rearrangement leads to:

$$P_{app} \left[1 + \frac{Ka}{[H_3O^+]} \right] = P_u + P_i \frac{Ka}{[H_3O^+]} \qquad 5.15.$$

Hence, using data for P_{app} against $[H_3O^+]$, a plot of P_{app} $\left[1 + \frac{Ka}{[H_3C^+]} \right]$ against $\frac{Ka}{[H_3O^+]}$ should yield a straight line with slope P_i and intercept P_u. If P_i is small, then P_{app} at any pH can be obtained by putting $P_i = 0$

$$P_{app} = P_u \left[\frac{1}{1 + K_a/[H_3O^+]} \right] \qquad 5.16.$$

For diffusion of the drug through the Alginate gel matrix to be the rate controlling step in mass transfer, then P_{app} should be sufficiently high for sink conditions to be maintained.

5.3   Materials and Methods

5.3.1 Diffusion Experiments

5.3.1.1 Apparatus and Protocol

The apparatus used to monitor the diffusion of Ibuprofen in various concentrations of Calcium Alginate gels is shown schematically in Figure 5.2.. The cell consisted of a jacketted glass beaker of internal diameter 6.6 cm. which allowed thermostatic control at $25°C$[1] . Initially, 50 cm^3 of Borate Buffer B.P. pH 7.5 containing Sodium Alginate[2] and Ibuprofen 0.5 mg cm^{-3} , was poured into the cell. Borate buffer was used as an alternative to the phosphate buffers usually employed at pH 7.5 because the presence of Calcium would cause precipitation. On top of this solution, a layer of dialysis membrane[3] was placed by covering one end of a perspex cylinder such that a close fit was achieved with the vessel wall. Stretching the membrane over the end of the cylinder ensured that the surface of the resulting Alginate gel was flat. Any entrapped air, was removed by sliding a fine stainless steel, blunt ended needle between the membrane and the vessel wall, and withdrawing air through a syringe.

1.   Churchill Thermocirculator
2.   Protonal LFR5/60: same batch as used previously.
3.   Visking 10 cm dry dia.tubing.

Figure 5.2   APPARATUS FOR THE DETERMINATION OF DIFFUSION
              COEFFICIENTS OF IBUPROFEN THROUGH ALGINATE GEL.

(a)   Dialysis Step

— Glass stirrer

— Perspex cylinder

— Water jacket at 25°C

— 100 cm^3 Ca^{2+} solution

— 'Visking' membrane

— 50 cm^3 Alginate Solution
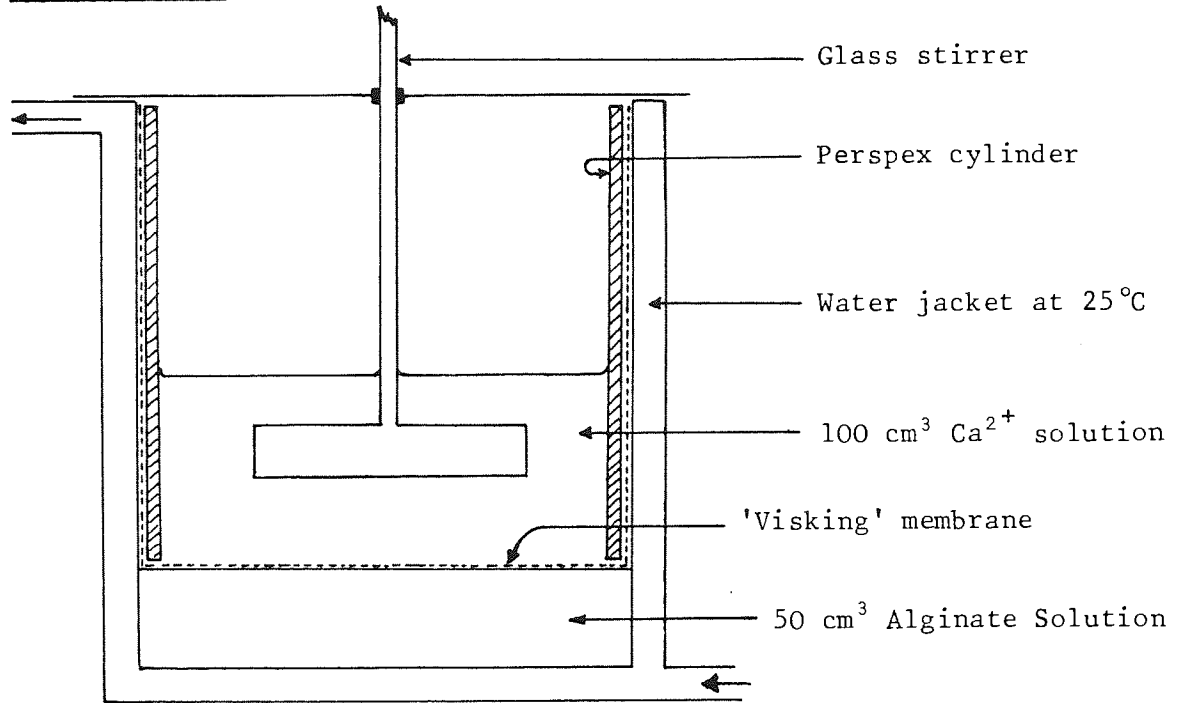
Dialysis 48 hr.

(b)   Diffusion Step

Sample

Replace

— Stirring at 100   rpm

— 50 cm^3 n-Octanol

— 50 cm^3 rigid Calcium
     Alginate gel
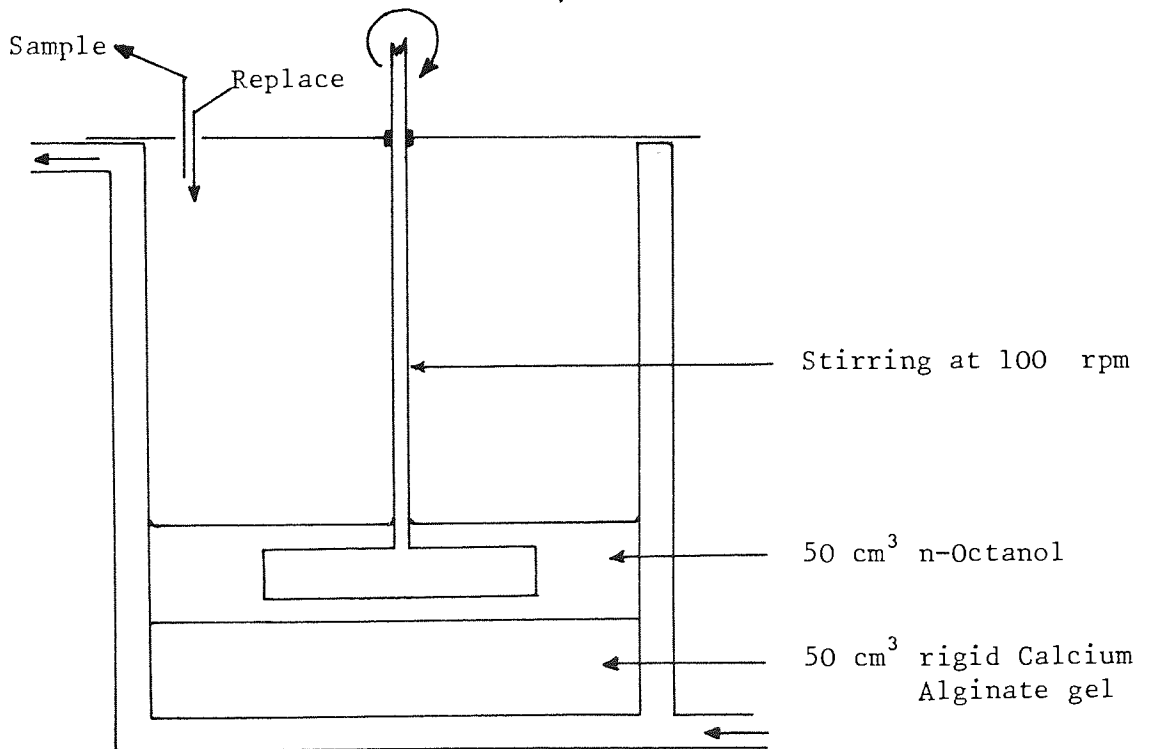
Above the membrane and within the cylinder was added 100 cm^3 of Borate buffer containing Ibuprofen 0.5 mg cm^{-3} and a known concentration of calcium chloride[1] . Dialysis with stirring of the upper phase was then carried out for 48 hr.

In order to obtain a flat, circular area of membrane in contact with the Alginate solution, it was necessary to force a fraction of the solution up between the vessel wall and the dialysis membrane. On withdrawal of the membrane after 48 hr., this excess Alginate, by then in gel form, was removed; it represented up to about 3% of gel by weight.

After dialysis, the dialysate, perspex cylinder and dialysis membrane were all removed from the cell and replaced by 50 cm^3 of n-octanol[2] . The initial concentration of Ibuprofen in the gel phase was checked by assaying the dialysate and applying mass balance. A solution of Ibuprofen 0.5 mg cm^{-3} which was stirred in the presence of dialysis membrane for seven days at room temperature showed no decrease in the assayed Ibuprofen concentration, therefore there appeared to be no significant interaction. The thickness of each phase, gel and n-octanol was approximately 1.5 cm and the latter phase was stirred at 100 rpm.[1] with a glass paddle stirrer 3.8 x 1.0 cm.. 1 cm^3 samples of the n-octanol phase were removed from a consistent position at various time intervals and replaced by 1 cm^3 of clean n-octanol.

1.   Ca Cl_2 . 6 H_2 O, Laboratory Reagent, BDH
2.   Analytical Reagent, Fisons.
3.   Citenco variable speed motor.

5.3.1.2 Dialysis Method of Gel Formation

The method by which an Alginate gel is formed may be
important in determining its characteristics. Sudden mixing
of a calcium ion solution with an Alginate solution will lead
to precipitation or at least heterogeneity of gel formation
and syneresis (15, 105). This is due to a rapid, localised
ie, autoco-operative binding of Ca^{2+} in certain regions of the
Alginate solution where calcium is most concentrated. Hence,
the reaction must be slowed down so that there is a gradual
supply of Ca^{2+} ions throughout the Alginate solution. This
can be achieved by dialysis or chemical means. The latter
method will be dealt with in Section 5.3.2.2..

The dialysis method has been extensively used by Smidsrød
et al (15, 240) for measuring the rigidity of gels formed
using various Alginates and divalent metal ions. They
determined the conditions for a state of 'practical
equilibrium' of the Alginate gels by measuring rigidity and
decrease in gel volume as a function of dialysis time. They
therefore determined the time necessary to ensure that
dialysis was complete.

To determine the conditions necessary to achieve a 'practical
equilibrium' for Calcium Alginate gels in the diffusion cell,
the dialysis system may be compared with that of Smidsrød
et al. These workers produced gels in a cylinder of height
1.5 cm and internal diameter 1.4 cm. The Alginate solution
was contained in the cylinder by sealing at each end with a

dialysis membrane. Dialysis took place in 4 x 50 cm^3 of 0.34 M

calcium chloride solution. It was found that the gel rigidity

increased rapidly but showed no change after 24 hr. dialysis;

gel volume decreased rapidly during the first 24 hr., but

showed little change in the next 12 days. Therefore, it was

assumed that for practical purposes, a state of equilibrium

was reached after 48 hr. dialysis.

The time taken to reach 'practical equilibrium' depends on

the exposed membrane area, A, the maximum distance that Ca^{2+}

ions are required to travel, h_{max} , and the member of Ca^{2+}

ions present, N_{Ca} . This assumes that transfer of Ca^{2+}

ions to and across the dialysis membrane are not rate-

determining. Smidsrød et al used Alginate with an intrinsic

viscosity, $[\eta]$ of 1.24 x 10^3 cm^3 g^{-1} , in concentrations of

up to 5.0 g dl^{-1} . From Section 2. 4 ., Protonal LFR5/60

used in the present study was found to have $[\eta]$ = 105

cm^3 g^{-1} and for dialysis, concentrations of 0.25 to 5.0 g dl^{-1}

were used.

A low value of h_{max} and $[\eta]$, and high values of A and N_{Ca}

are favourable for a short dialysis time. This can be

quantified by using a proportionality constant R' such that

$$t_d = \frac{R' \, h_{max} \, [\eta]}{A \, N_{Ca}}$$
5.17

where td = dialysis time required to achieve 'practical
equilibrium'.

N_{Ca} = molar concentration of Ca^{2+} multiplied by
the volume of dialysate.

Assuming that Smidsrød et al (240) changed the 50 cm^3 of

dialysate four times during the experiment, only 50 cm^3

was present at any one time. Substituting h_{max} = 0.75 cm,

A = $2\pi(0.7)^2$ cm^2, N_{Ca} = 0.34 x 10^{-3} x 50 Mol, t_d =

24 hr., and $[\eta]$ = 1.24 x 10^3 cm^3 g^{-1}, then R' = 1.35 x

10^{-3} g Mol hr cm^{-2} .

If corresponding values are substituted for the experimental

system detailed in Section 5.3.1.1., then t_d can be

determined. Two strengths of Ca^{2+} solution were used:

0.1 M for Alginate concentrations of less than 3.0 g dl^{-1} and

0.4 M for 3.0 and 5.0 g dl^{-1} of Sodium Alginate. Hence, N_{Ca}

= 0.01 and 0.04 mol respectively. Other quantities are h_{max}=

1.5 cm, A = $\pi(3.3)^2$ cm^2 and $[\eta]$ = 105 cm^3 g^{-1} .

Therefore, t_d = 0.6 and 2.5 hr for N_{Ca} = 0.01 and 0.04 mol

respectively. From these results, it was concluded that a

dialysis time of 48 hr. was ample to ensure that a 'practical

equilibrium' existed.

Because of a possible detrimental effect on the dialysis

membrane, the Alginate solution and dialysate were not pre-

saturated with n-octanol. This would cause a slight

discrepancy between the apparent partition coefficient as

calculated from the absolute coefficients, and the apparent

partition coefficient found from the asymptote of the

experimental drug release profile.

In addition to this, the osmotic effect dictates that water

will tend to pass into the dialysate Ca^{2+} solution from the
Alginate phase if the chemical potential, or concentration,
of the solvent molecules is greater in the latter than the
former.

5.3.1.3 Effect of Stirrer Speed

For the mechanism of drug release from the Alginate gel to
be diffusion and not partitioning of the Ibuprofen into the
n-octanol phase, then mass transfer should be independent of
the stirrer speed   with 0.1 M Ca^{2+}
being dialysed against a 1.0 g dl^{-1} solution of Sodium
Alginate. Five experiments using a stirrer speed of 100 rpm
were compared with corresponding experiments using 50 and
150 rpm stirrer speeds.

5.3.1.4 Concentration Gradient within the Gel

Since the Ibuprofen is in solution in the gel phase, then
transfer into the n-octanol phase is rate-limited either by
diffusion through the gel or partitioning between the aqueous
and organic phases. To discern which is the dominating
mechanism, duplicate experiments were carried out using the
regimen given in Section 5.3.1.1. The initial Sodium Alginate
concentrations used were 1.0 and 5.0 g dl^{-1} dialysed against
0.1 and 0.4 M Ca^{2+} respectively. After a time corresponding
to about 50% of drug transfer, each gel was removed and sliced
laterally, using a sharp blade, into five approximately equal
0.3 cm fractions. Particular care was necessary because of
the brittle nature of the gel. Each slice was weighed, then

182

the Ibuprofen extracted with excess 0.5 M HCl and 5 cm^3

of n-octanol. The n-octanol phase was then assayed, using the

HPLC method detailed in Section 5.3.4.

5.3.2 Rheological Experiments

5.3.2.1 The Use of Oscillatory Rheometry.

In Section 2.2.3., the principles of each of the three major

methods of rheological testing, namely continuous shear, creep

and oscillatory testing, were considered. The continuous

shear method does not lend itself to the measurement of

elastic solids such as Alginate gels. This is not only

because the data produced in the form of a shear stress -

shear rate curve cannot be interpreted in terms of elasticity,

but also because the gel is liable to fracture when subject to

high shear rates.

The method of creep testing was used by Mitchell and Blanchard

(105) with a parallel plate viscometer designed by Sharma

and Sherman (241). The creep compliance - time response was

fitted by a mechanical model with a Maxwell element in series

with two or three Voigt elements.

Nevertheless, the use of low amplitude oscillatory shear

testing is particularly suited to samples of a brittle nature

since the net deformation during testing is negligible.

Apart from a brief investigation into the application of the

theory of ideal rubber-like elasticity (242) to Alginate gel

systems (243) results from the oscillatory shear testing of
Alginate gels have not been published. In the present study,
parallel plate geometry was used to quantify the rigidity of
Calcium Alginate gels containing 0.25 to 5.0 g dl^{-1} of
Alginate (calculated as the sodium salt) and 0.01 to 0.1 M
Ca^{2+} . The experimental regimen using the Weissenberg
Rheogoniometer was the same as that detailed in Section
2.3.5.. The input amplitude of the lower platen was
2.8 x 10^{-3} rad.

5.3.2.2 Chemical Method of Gel Formation

In Section 5.3.1.2, it was pointed out that a gradual supply
of $Ca^{2+}$is necessary in the Alginate solution if a homogeneous
Calcium Alginate gel is to be formed. As an alternative to
dialysis, Mitchell and Blanchard (104) first employed Glucono-
δ-lactose, GDL, to form Alginate gels in a matter of minutes
instead of days. In aqueous solution, GDL is gradually
hydrolysed to gluconic acid, see Figure 5.3.. A freshly
prepared 1.0 g dl^{-1} solution has a pH of 3.6 which falls to
2.5 within 2 hr. (244).

Figure 5.3   The Hydrolysis of Glucono-δ-Lactone in Water

Glucono-δ-Lactone   Gluconic Acid
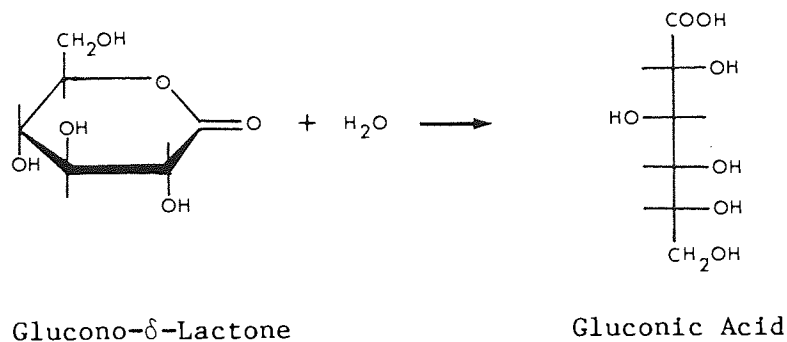
When preparing samples of Calcium Alginate for rheological

testing, the dialysis method was inappropriate due to

manipulative difficulties in preparing a gel of the

appropriate dimensions. To overcome this problem, the GDL

method was used as follows. A freshly prepared solution of

GDL was added to a dispersion of Calcium Hydrogen Phosphate,

$CaHPO_4$, in Sodium Alginate solution, the volume ratio of

the former to the latter being 1:3. Stirring with a magnetic

follower ensured rapid mixing and gelling usually took place

within 2 min.

Samples for rheogoniometry were prepared by pouring the

mixture prior to gelling, into polyethylene petri dishes.

After gelation, circular gels of exactly 7.5 cm diameter were

cut using a bladed tin template. This ensured that each

sample exactly fitted between the rheogoniometer parallel

plates. The thickness of the gel sample was not critical in

parallel plate geometry since this is taken into account in

the calculation of G', see Equation 2.25..

To determine their effect on gelation, the pH of the resulting

gels was measured for various concentrations of

ingredients GDL,   and Alginate.

Since the GDL causes gel formation by lowering the pH to allow

calcium salt dissolution, the resultant gel may be dependent

on the presence of H^+ ions as well as the Na^+ replacement

by Ca^{2+} ions. This would be likely to occur close to the

pKa of the Alginic acid. The method of Haug (245) was used
to determine the overall pKa of Alginic acid from Protonal
LFR5/60 Sodium Alginate. Mannuronic and guluronic acids have
pKa's of 3.38 and 3.65 respectively (1), therefore one may
expect the Alginic acid copolymer to possess an overall pKa
somewhere between these two values. Haug used a modified form
of the Henderson-Hasselbach Equation as follows:

$$pH = pKa + n \log \left[\frac{\alpha}{1 - \alpha} \right]$$
5.18

where α = degree of neutralisation

$$n = \text{activity correction} = \left\{ \frac{f_{H_3O^+} \quad f_{A^+}}{f_{HA}} \right\}$$
5.19

Alginic acid was prepared by precipitation with excess 0.5 M
HCl in a 12.0 g dl^{-1} solution of Sodium Alginate and stirring
for 8 hr. The precipitate was rinsed thoroughly with
distilled water and dried at 50° C for 48 hr. A range of
volumes of 0.1 M NaOH and 0.1 M NaCl (the latter to ensure
constant ionic strength) were added to 20 cm^3 aliquots
containing exactly 0.1 g of Alginic acid thereby giving
0.0258 molar Alginate based on an equivalent weight of 194 g
mol^{-1} . After addition of the alkali, the samples were placed
in a shaking water bath at 25° C for 6 hr. and their pH values
were determined.

5.3.3 Partition Coefficient of Ibuprofen

The derivation of Equation 5.15. by Irwin and Li Wan Po
(206) for the determination of the partition coefficients

of ionised and unionised species was given in Section 5.2.2.. The experimental determination of P_{app} for Ibuprofen was carried out as follows. Eight solutions of Ibuprofen 0.5 mg cm^{-3} in Kolthoff's buffer (246) were used in the pH range 8.02 to 9.19, with the ionic strength adjusted to 1.5 using KCl. Distilled water that had been pre-saturated at $25°C$ with n-octanol was used to make these solutions and duplicates were prepared of each sample. 20 cm^3 of aqueous phase was added to 5 cm^3 of n-octanol that had been pre-saturated with water. To avoid emulsification, the specimen tubes were inverted gently several times and placed in a slowly shaking water bath at $25°C$ for 13 days.

At the end of this time, the concentration of Ibuprofen in the aqueous and organic phases was measured using the HPLC method described in Section 5.3.4., from which P_{app} could be calculated.

5.3.4 HPLC Assay of Ibuprofen

The method used to assay Ibuprofen in n-octanol was based on the work of Dusci and Hackett (247) who used a reversed-phase High Performance Liquid Chromatographic, HPLC, system. Acetonitrile, CH_3CN with water mobile phases were used to separate seven anti-inflammatory drugs in serum. Ibuprofen eluted at 5.4 min when 35% CH_3CN in 0.7% aqueous ammonium chloride solution adjusted to pH 7.8 was used as the mobile phase. The flow rate was 1.0 cm^3 min^{-1} using a 30 cm x 0.39 cm I.D. Column packed with μBondapak C_{18} .

In another mobile phase system, 60% CH_3CN, 45 mM KH_2PO_4 adjusted to pH 3.0 was used with a flow rate of 0.8 cm^3 min^{-1} Ibuprofen was eluted at 8.6 min.

Ali et al (248) used a similar column to that of Dusci and Hackett, and found that a mobile phase of 55% CH_3CN in 0.1M acetic acid pumped at 1.0 cm^3 min^{-1} gave a retention time for Ibuprofen assayed in plasma, of 8.5 min.

In the present study, using a 25 cm x 0.4 cm. I.D. column containing 10 μm C_{18} bonded Partisil ODS-2[1] , a suitable mobile phase was found to be 72% CH_3CN[2] in distilled water adjusted to pH 3.0 with phosphoric acid. The mobile phase flow rate was 1.0 cm^3 min^{-1}.[3] The octanolic drug solution was diluted 1:1 with methanol[4] containing 20 μg cm^{-3} of benzoic acid[5] as internal standard. The sample was injected into the column via a 20 μl injector loop[6] and the eluted compounds were detected by UV at 225 nm[7] . Calibration lines of six samples in the appropriate concentration range were performed on each occasion of use.

1.   Whatman, Maidstone, UK.
2.   Acetonitrile, HPLC grade, Fisons
3.   Altec 100A Pump, Anachem, Luton, U.K.
4.   Methanol, HPLC grade, Fisons
5.   Analytical Reagent grade, BDH, Poole, UK.
6.   Rheodyne, Berkeley, California, USA.
7.   Pye Unicam LC3 Detector, Cambridge, UK.

Figure 5.4. shows a typical trace of the resultant chromatogram. The retention times were 1.3, 3.6 and 5.1 min for benzoic acid, Ibuprofen and n-octanol respectively. Analytical reagent grade of n-octanol was employed since the use of a spectroscopic grade did not significantly reduce the size of the broad peak due to n-octanol which eluted after Ibuprofen.

The methonol: water mobile phases used by Pitrè and Grandi (249) and Thomas et al (250) produced very broad peaks using the above equipment despite variation in the methanol: water ratios.

The use of the above system with 72% CH_3CN at pH 3.0 for the mobile phase provided a significant reduction in retention times compared to previous methods.

Figure 5.4

A TYPICAL HPLC TRACE
FOR IBUPROFEN ASSAY
IN N-OCTANOL: METHANOL,
1:1.

a.u.f.s. = 0.16

λ = 225 nm

Injection volume 20 μl

1. Injection
2. Solvent front
3. Benzoic acid 30 μg cm^{-3}
4. Ibuprofen 50 μg cm^{-3}
5. n-Octanol

Sample

Solvent
only
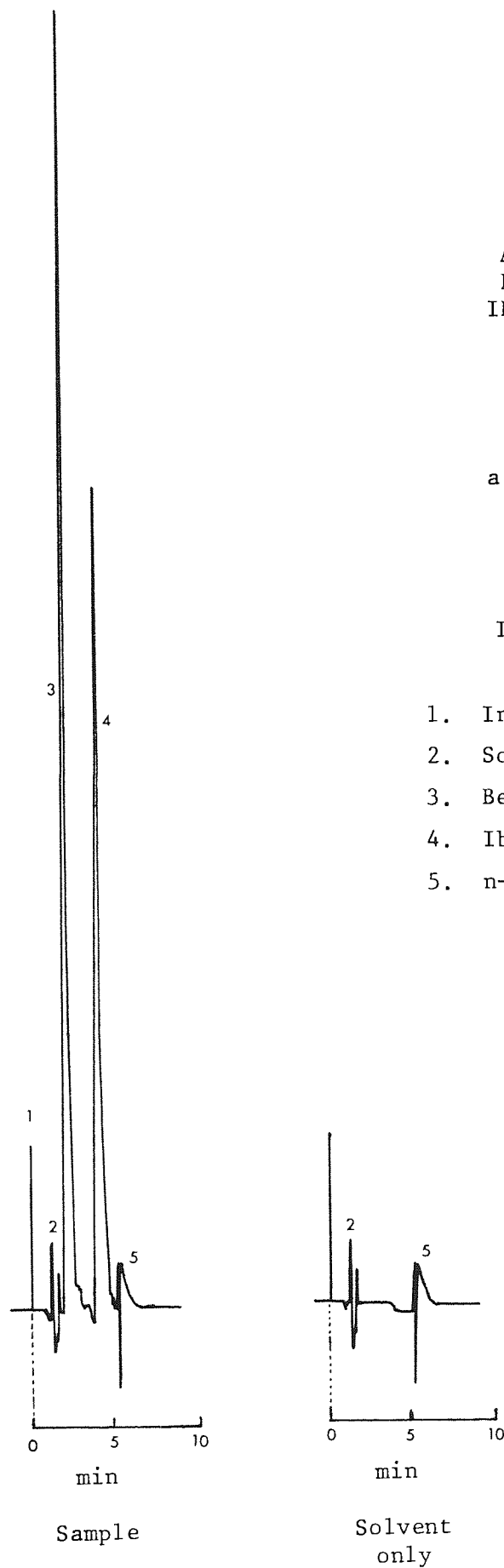
5.4 Results

5.4.1 Partition Coefficient of Ibuprofen

Using the method given in Section 5.3.3., values of P_{app}

for Ibuprofen as a function of pH were obtained. This data

was transformed according to Equation 5.17.. The results are

listed in Table 5.1.. The value of the pKa of Ibuprofen at

$25\,^{\circ}C$ used was 4.45 (251) which is in good agreement with a

value of 4.5 quoted elsewhere (252). The plot of P_{app}

$(1 + K_a/\ [H_3O^+\ ])$ as ordinate against $(K_a /\ [H_3O^+])$ shows

good linearity, see Figure 5.5.. The least mean square linear

correlation coefficient was 0.996; the slope, $P_i = 0.476$

and the intercept, $P_u = 9.07 \times 10^3$. From Equation 5.17.,

P_{app} at pH 7.5, the pH of the buffered Calcium Alginate gel

in diffusion experiments, was calculated to be 8.55. However,

after the dialysis step, the pH of a 5.0 g dl^{-1} Alginate gel

(calculated as the sodium salt), was found to be as high as

7.85, which corresponds to $P_{app} = 4.1$. The high pH was

probably due to the presence of Alginate, although measurement

of the pH of a rigid gel is prone to inaccuracies because of

poor mixing and poor contact with the electrode. The

deviation from pH 7.5 was less significant for lower Alginate

concentrations.

When diffusion experiments using a 5.0 g dl^{-1} Alginate gel

were carried out to completion, ie, the concentration of

Ibuprofen in n-octanol became asymptotic with time, then

values of $P_{app} \simeq 4.0$ were found, see also Section 5.4.2.3..

This result was consistent with a gel pH of approximately 7.9.

Table 5.1. Results for the Determination of the Ionised and Unionised Partition Coefficients of Ibuprofen.

pH	Mean Concentrations ($\mu g\ cm^{-3}$)		Assay as % of theoretical concentration	P_{app}	$\dfrac{K_a}{[H_3O^+]} \times 10^{-3}$	$P_{app} \left\{ 1 + \dfrac{K_a}{[H_3O^+]} \right\} \times 10$
	Aqueous Phase	n-Octanol Phase				
8.02	290.5	706.0	96	2.602	3.715	9.671
8.18	382.8	734.5	103	2.207	5.370	11.85
8.38	362.3	553.2	100	1.527	8.511	12.99
8.59	412.9	475.2	106	1.151	13.80	15.89
8.78	399.6	373.5	99	0.935	21.38	19.99
9.01	440.9	328.8	105	0.746	36.31	27.08
9.12	441.0	302.5	103	0.686	46.77	32.08
9.19	443.2	273.0	102	0.616	54.95	33.85

Figure 5.5.

DETERMINATION OF THE IONISED AND UNIONISED
PARTITION COEFFICIENTS OF IBUPROFEN IN WATER/
n–OCTANOL AT 25°C

$P_{app}\left\{1 + K_a/[H_3O^{\oplus}]\right\} \times 10^{-3}$

$\left\{K_a/[H_3O^{\oplus}]\right\} \times 10^{-3}$
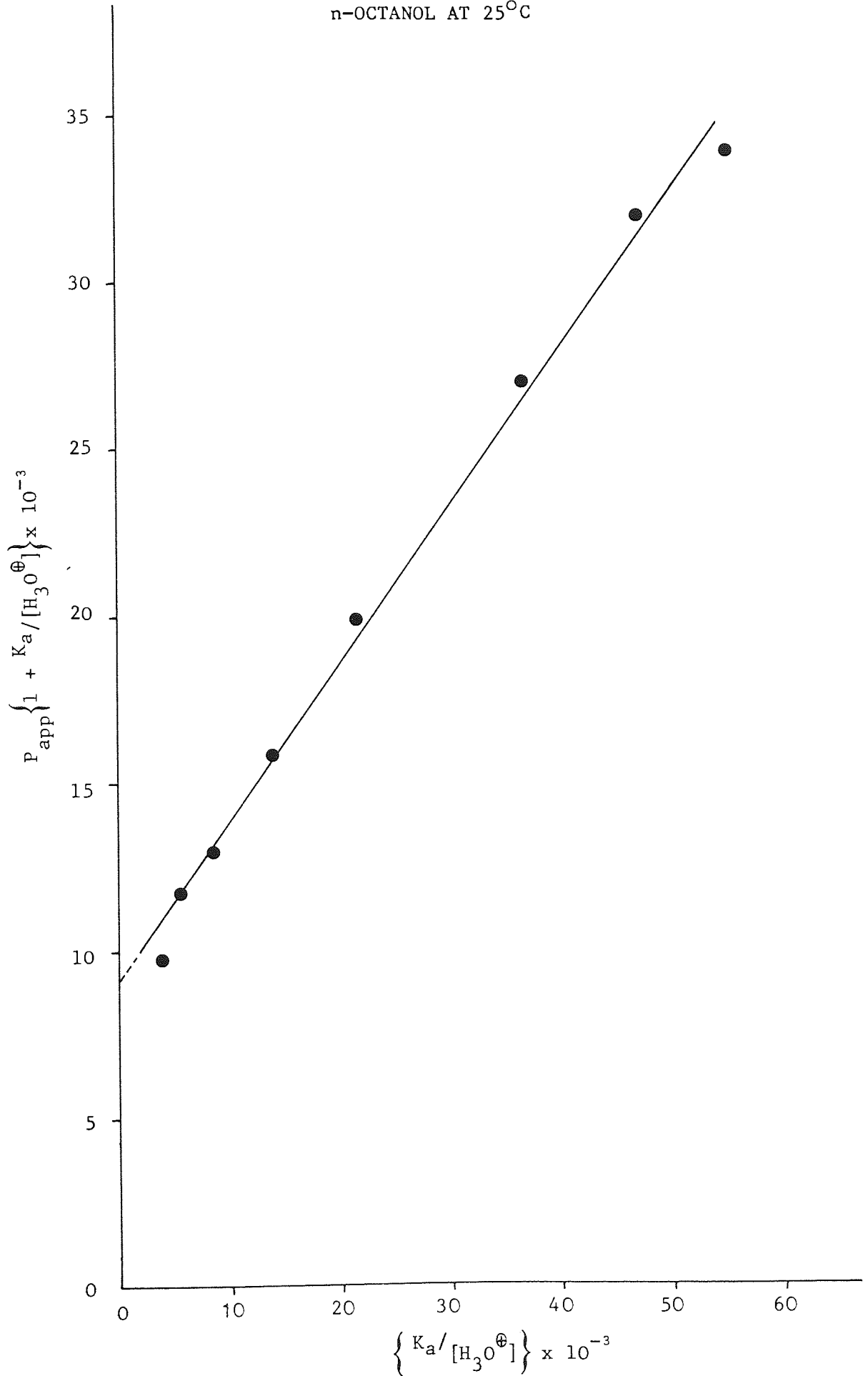
5.4.2 Diffusion Experiments

5.4.2.1 Effect of Stirrer Speed

Using the protocol outlined in Sections 5.3.1.1 and 5.3.1.3, five experiments were carried out with a stirrer speed of 100 rpm. To compare the rate of drug release at different stirrer speeds by a consistent method, data for less than 50% released was applied to the square root approximation, Equation 4.4., by plotting the amount transferred per unit area at time t, ie Q, against $t^{\frac{1}{2}}$. From the slope, K, values of the diffusion coefficient were obtained using the equation:

$$D = \frac{\pi}{4} \left(\frac{K}{C_o}\right)^2 \qquad\qquad 5.20.$$

At 100 rpm, $D = 5.11 \pm 0.54 \times 10^{-6}$ cm^2 sec^{-1} (mean $\pm$ 95% confidence limits) whereas at 50 rpm, $D = 3.13 \times 10^{-6}$ cm^2 sec^{-1} . Hence, D at 50 rpm is significantly less than D at 100 rpm $(P > 0.999)$.

Using a stirrer speed of 150 rpm, $D = 5.01 \times 10^{-6}$ cm^{2}sec^{-1} was obtained; this was not significantly different from D for 100 rpm stirrer speed. These results suggest that mass transfer was partition-controlled at 50 rpm but not at 100 or 150 rpm stirrer speeds. Subsequently, the 100 rpm speed was used in all experiments.

5.4.2.2 Concentration Gradient Within the Gel.

Using the protocol detailed in Sections 5.3.1.1 and 5.3.1.4, it was possible to obtain values for the concentration of Ibuprofen in the gel as a function of the distance from the interface with the n-octanol. The results are listed in Tables 5.2. (a) and (b). The figures show that a significant concentration gradient existed in the gel which suggests that diffusion was the rate-controlling mechanism of drug release.

Unfortunately, due to the brittle nature of the gel, it was not possible to obtain a sufficient number of values of concentration as a function of distance in the gel, to apply the relationship for unsteady state diffusion, ie, Equation 4.28.. However, bearing in mind the findings of the numerical analysis of Section 4, it is possible to apply correctly the square-root-time approximation, Equation 4.4., to describe drug release data for less than 50% release.

Table 5.2. The Concentration of Ibuprofen in the Gel Phase as a function of the Distance from the Interface.

(a) Gel Containing 1.0 g dl^{-1} Alginate

Mean Distance from Interface (cm)	Weight of Gel Sample (g)		Extracted Concentration (μg cm^{-3})		Concentration of Ibuprofen in Gel Fraction (μg cm^{-3})		
	1	2	1	2	1	2	Mean
0.15	5.052	2.007	58.2	63.5	57.6	63.3	60.4
0.45	5.210	1.748	102.8	114.9	98.7	131.5	115.1
0.75	4.448	1.745	122.5	165.4	137.7	189.6	163.6
1.05	3.391	1.945	110.3	212.5	162.6	218.5	190.6
1.35	3.975	2.300	122.3	252.8	153.9	219.8	186.8

(b) Gel Containing 5.0 g dl^{-1} Alginate

Mean Distance from Interface (cm)	Weight of Gel Sample (g)		Extracted Concentration (μg cm^{-3})		Concentration of Ibuprofen in Gel Fraction (μg cm^{-3})		
	1	2	1	2	1	2	Mean
0.15	6.011	2.212	83.3	51.4	69.3	46.5	57.9
0.45	6.199	1.882	84.1	80.3	67.9	85.8	76.5
0.75	6.774	1.956	155.6	151.0	134.8	154.4	144.6
1.05	6.196	3.025	221.5	263.1	178.7	173.9	176.3
1.35	6.538	2.575	264.5	258.6	202.3	200.8	201.6

5.4.2.3 Drug Release Profiles

A range of concentrations of Sodium Alginate from 0.25 to
5.0 g dl^{-1} was used to obtain Calcium Alginate gels by
dialysis. The concentration of Ibuprofen released from
the gel into the n-octanol phase was monitored with time.
After correction for solute loss due to sampling, values
for the amount released were divided by the interfacial
area. A, to obtain Q, the amount released per unit area.
The collective results for those diffusion experiments are
given in Tables 5.3. to 5.7. for 0.25, 0.50, 1.0, 3.0 and
5.0 g dl^{-1} Alginate gels respectively.

Since the initial concentration of Ibuprofen in the gel,
ie, C_O., is squared in Equation 5.22. its determination
needs to be accurate to obtain realistic values of D. After
dialysis, the volume and Ibuprofen concentration of the
dialysate was determined and by mass balance, the concentrat-
ion in the gel was calculated. The mean value of C_O for all
20 experiments quoted was 492.1 μg cm^{-3} with a standard
error of 3.6% and 95% confidence limits of $\pm$ 8.2 μg cm^{-3} .
Hence, the initial concentration in the Alginate gel was not
significantly different from the value of 500 μg cm^{-3}
expected.

A specimen drug release profile is given in Figure 5.6.
where the concentration of Ibuprofen in n-octanol is
followed to equilibrium. The Alginate concentration
50 g dl^{-1} . The curve appears to become asymptotic after

Table 5.3   Experimental Data for the Diffusion of Ibuprofen
in 0.25 g dl^{-1} Alginate Gels.

Time (Min)	Amount Released per Unit Area (μg cm^{-2})			
	1	2	3	4
10	–	–	39.41	40.41
15	41.87	38.50	–	–
20	–	–	55.14	62.76
30	61.80	53.97	66.37	70.96
45	75.76	74.94	78.41	74.45
60	86.10	83.86	89.76	93.12
90	104.7	102.9	108.2	108.1
120	120.2	117.0	121.9	124.1
150	121.1	112.7	130.8	130.1
180	141.1	136.7	143.8	139.7
210	–	–	150.5	147.6
270	–	–	166.8	170.5
300	183.4	179.2	–	–
360	194.7	199.2	191.4	191.1
420	207.8	206.4	202.7	200.8
450	218.8	221.7	216.9	215.1
540	227.4	225.0	230.5	222.4
600	235.7	233.4	238.7	234.8
Interfacial Area, A (cm^2)	33.9	33.9	33.9	33.9
C_O (μg cm^{-3}) *	505.7	505.7	487.5	491.4

* C_O = Concentration of Ibuprofen in the gel phase at time zero.

Table 5.4   Experimental Data for Diffusion of Ibuprofen in
0.50 g dl^{-1} Alginate Gels.

Time (Min)	Amount Released per Unit Area ($\mu g \ cm^{-2}$)	
	1	2
15	39.62	38.51
30	56.90	52.68
45	69.32	66.68
60	82.14	77.27
90	96.77	94.90
120	113.7	109.6
210	145.9	159.3
250	155.3	162.5
310	170.7	172.6
360	182.7	184.8
420	194.4	195.3
480	199.1	–
540	213.2	210.8
600	214.5	221.6
Interfacial Area, A (cm^{-2})	33.9	33.9
C_O ($\mu g \ cm^{-3}$) *	464.7	472.1

* C_O = Concentration of Ibuprofen in the gel phase at time zero.

Table 5.5 Experimental Data for Diffusion of Ibuprofen in
1.0 g dl^{-1} Alginate Gels.

Time (min)	Amount Released per Unit Area (μg cm^{-2})					
	1	2	3	4	5	6 [†]
15	40.23	38.88	41.43	47.46	47.72	37.69
30	56.49	50.73	57.60	64.39	66.23	54.33
45	66.40	61.87	68.71	82.94	70.67	61.78
60	77.37	69.65	78.16	91.26	84.62	76.17
90	95.67	81.67	93.57	103.3	102.0	91.58
120	110.5	104.8	106.8	–	115.1	106.6
150	120.9	–	118.3	123.2	126.4	–
180	136.6	124.6	128.9	143.9	138.5	133.9
240	159.7	136.9	157.8	161.8	158.0	164.6
300	175.9	160.3	177.5	180.5	181.2	177.4
360	201.1	172.1	188.9	–	199.5	189.4
420	216.2	183.9	199.4	192.0	217.4	191.2
480	224.0	191.5	–	202.8	235.6	210.1
540	–	204.6	222.6	222.6	–	216.0
600	–	215.1	231.5	243.8	255.8	224.3
Interfacial Area, A (cm^{-2})	34.2	34.2	34.2	34.2	34.2	34.2
C_O (μg cm^{-3})*	507.0	461.2	481.3	465.5	501.4	478.9

[†] Experiment conducted using 150 rpm stirrer speed, see Section
5.4.2.1..

* C_O = Concentration of Ibuprofen in the gel phase at time zero.

Table 5.6. Experimental Data for Diffusion of Ibuprofen in 3.0 g dl^{-1} Alginate Gels.

Time (Min)	Amount Released per Unit Area (μg cm^{-2})			
	1	2	3	4
16	42.67	38.54	28.53	35.30
30	50.65	56.66	43.53	48.17
45	58.49	69.42	60.54	61.89
60	70.34	80.26	63.72	71.97
90	86.53	89.27	77.21	85.91
120	97.68	101.7	91.55	103.5
150	114.1	114.9	99.39	112.1
180	122.8	127.8	−	−
215	−	−	121.0	134.5
245	142.6	152.9	−	−
300	161.2	164.7	−	−
335	−	−	154.0	179.0
360	170.4	179.4	161.7	186.4
420	192.3	196.1	173.5	199.1
480	194.9	202.7	190.9	207.3
540	202.2	210.0	200.7	211.2
600	218.0	−	210.1	220.3
Interfacial Area, A (cm^{-2})	33.9	33.9	34.7	34.3
C_O (μg cm^{-3})*	502.2	503.1	495.9	485.1

* C_O = Concentration of Ibuprofen in the gel phase at time zero.

Table 5.7. Experimental Data for Diffusion of Ibuprofen in
5.0 g dl^{-1} Alginate Gels.

Time (min)	Amount Released per Unit Area (μg cm^{-3})			
	1	2	3	4
10	–	–	29.66	23.24
15	45.15	43.04	–	–
20	–	–	46.25	35.79
30	60.91	61.70	56.88	44.67
45	74.63	71.30	69.56	57.63
60	83.11	85.83	86.42	68.79
90	102.4	103.8	100.2	85.84
120	122.3	124.5	115.1	98.79
150	129.6	137.7	127.3	109.5
180	141.0	151.9	138.5	122.4
210	–	–	151.1	132.7
240	165.3	172.9	–	–
270	–	–	164.1	153.2
300	180.9	195.8	–	–
360	–	–	186.0	182.3
420	214.7	228.1	202.5	201.2
480	233.4	239.8	215.0	210.4
540	245.9	255.7	229.5	224.4
600	252.3	266.8	237.3	226.4
Interfacial Area, A(cm^{-2})	34.3	34.7	34.3	34.7
C_O*(μg cm^{-3})	491.2	498.1	518.4	524.2

* C_O = Concentration of Ibuprofen in the gel phase at time zero.

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Figure 5.7

THE AMOUNT RELEASED PER UNIT AREA, Q
PLOTTED AGAINST $(TIME)^{1/2}$ FOR DIFFUSION
IN A 5.0 g dl^{-1} ALGINATE GEL.

Slope, $K = 1.334$ μg cm^{-2} $sec^{-\frac{1}{2}}$

Q $(\mu g$ $cm^{-2})$

$\sqrt{t}$ $(sec)^{\frac{1}{2}}$
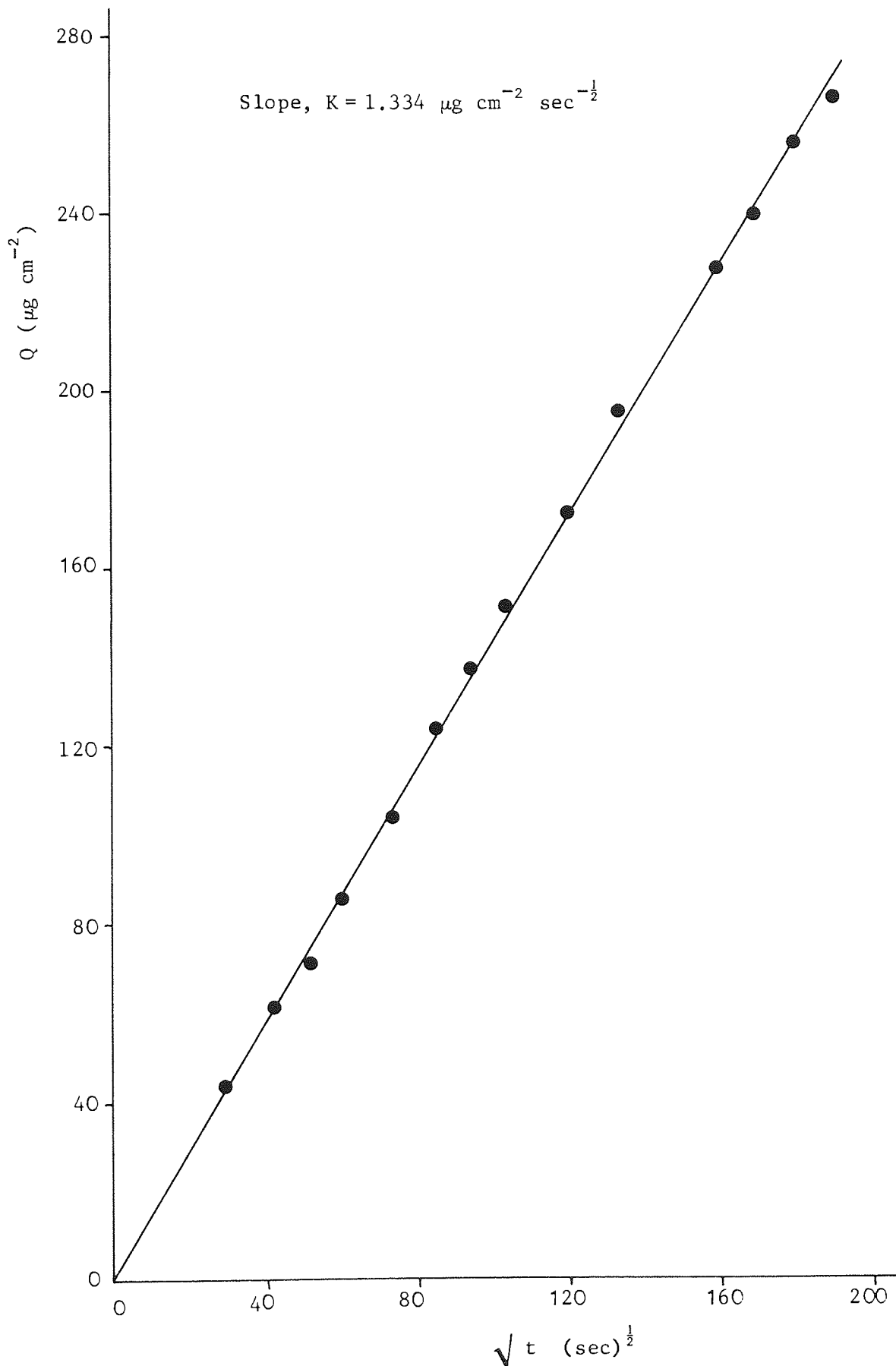
approximately 80 hr. at a concentration of approximately

400 μg cm^{-3} . 50% drug release took place within 14 hr.

A sample plot of Q against $t^{\frac{1}{2}}$ is given in Figure 5.7. for Ibuprofen diffusion from a 5.0 g dl^{-1} Alginate gel, which shows good linearity. The collective data for all such plots with least mean square linear regression analyses, is given in Table 5.8.. The diffusion coefficients obtained are summarized with 95% confidence limits, in Table 5.9.. It is clear from these results that the increasing concentration of Alginate did not significantly reduce the diffusion coefficient of Ibuprofen. This suggests that the microscopic viscosity in the gel was unaffected by increasing Alginate content and that the increasing number of polymer chains and cross-links was insufficient to cause mechanical blocking of the diffusant. This will be discussed further in Section 5.5..

Figure 5.6. Drug Release Profile for the Diffusion of Ibuprofen from a 5.0 g dl^{-1} Alginate Gel to a n-Octanol Sink.

Time (hr.)

Concentration of Ibuprofen in Octanol (μg cm^{-3})
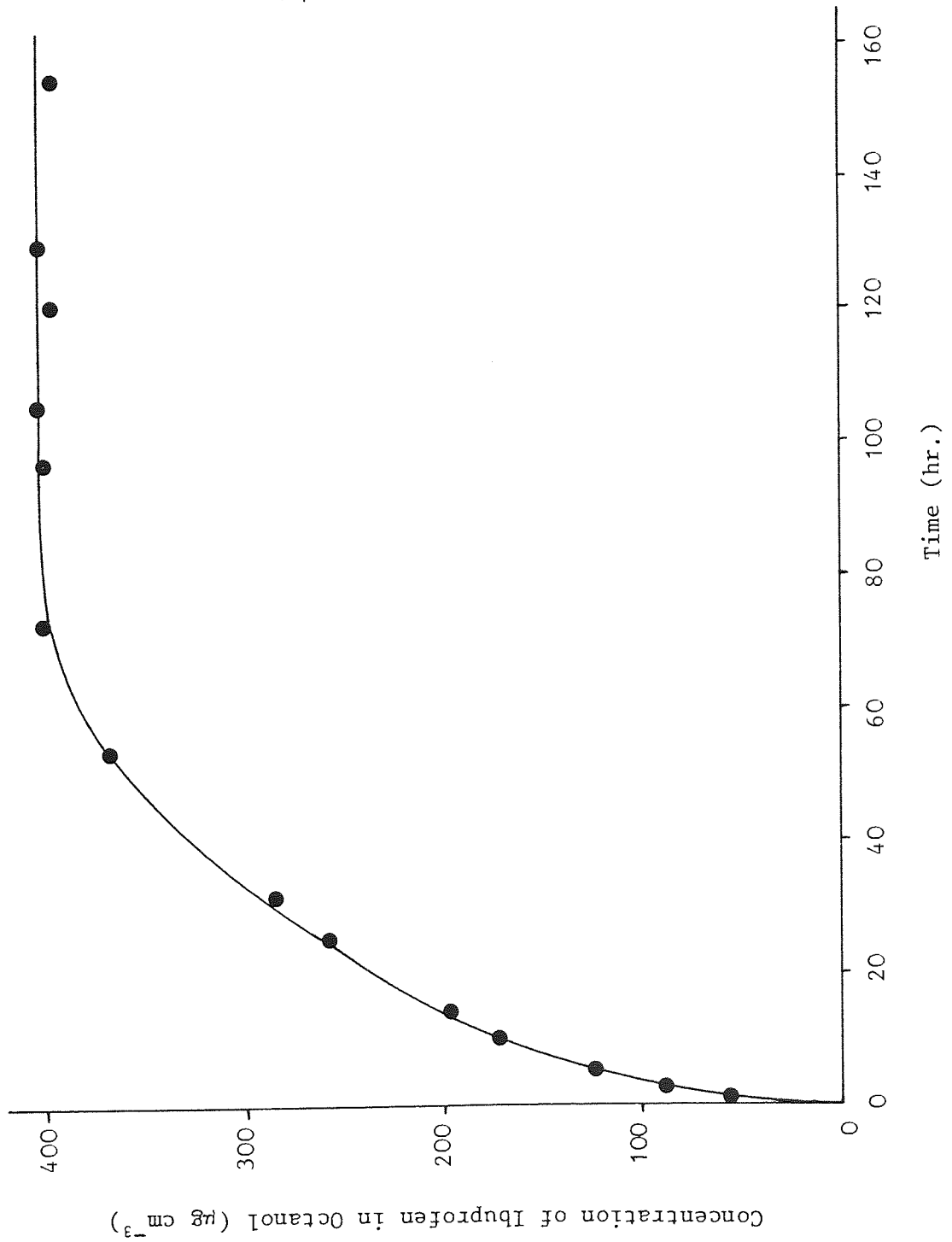
Table 5.8   Results of Linear Least Mean Square Regression
             Analysis of Data for the Amount of Ibuprofen
             Released per Unit Area, Q, against (Time)$^{\frac{1}{2}}$.

Alginate Concentration (g dl^{-1})	Correlation Coefficient	Slope, K (μg cm^{-2} sec$^{-1/2}$)	Intercept (μg cm^{-2})	Diffusion Coefficient, D (cm^2 sec^{-1}) x 10^6
0.25	0.9977	1.218	12.14	4.556
	0.9968	1.241	7.84	4.731
	0.9980	1.218	12.47	4.660
	0.9982	1.129	23.05	4.002
0.5	0.9961	1.119	13.51	4.556
	0.9916	1.175	8.73	4.849
1.0	0.9989	1.356	-3.31	5.618
	0.9986	1.122	4.39	4.650
	0.9982	1.222	5.21	5.063
	0.9951	1.143	19.12	4.736
	0.9986	1.326	4.40	5.493
	0.9946	1.210	4.61	5.013
3.0	0.9981	1.138	3.70	4.032
	0.9981	1.166	6.40	4.220
	0.9970	1.221	-1.56	4.759
	0.9991	1.132	-4.69	4.277
5.0	0.9986	1.243	6.24	5.026
	0.9990	1.274	-7.46	5.135
	0.9995	1.334	3.92	5.201
	0.9996	1.419	1.29	5.798

Table 5.9   Summary of Results for the Diffusion of Ibuprofen
                    in Calcium Alginate Gels.

Alginate Concentration (g dl^{-1}).	Mean Diffusion Coefficient (cm^{2}sec^{-1}) x 10^6	95% Confidence Limits	Number of Experiments
0.25	4.487	± 0.412	4
0.5	4.703	-	2
1.0	5.096	± 0.411	6
3.0	4.322	± 0.492	4
5.0	5.280	± 0.520	4

5.4.3 <u>Rheological Experiments</u>

5.4.3.1 <u>Effect of Glucono-δ-Lactone and Alginate</u>
<u>Concentrations on Calcium Alginate Gels.</u>

The chemical method of gel formation using Glucono-δ-Lactone, GDL, was examined according to the method given in Section 5.3.2.2.. The results for the effects of GDL and Alginate concentration on Calcium Alginate gels are given in Tables 5.10. and 5.11. respectively. It appeared that a concentration of 2.0 g dl^{-1} GDL was the maximum that would bring about gelation, therefore the pH needed to fall below 4.7 before gelation took place. If gelation occurred after the arbitrary 2 min., then the resulting gel was usually incompletely formed.

In the presence of low concentrations of Ca^{2+} ions, the resulting gels were weak, ie, the available sites for cross-linking were not saturated. The data is summarized in Figure 5.8. where it appears that Ca^{2+} Alginate has a relatively small effect on pH compared to GDL.

The dissociation constant for Alginic acid prepared from Sodium Alginate was determined according to the method give in Section 5.3.2.2.. The results for the pH at a function of the degree of neutralisation, α, are given in Table 5.12.. The value of $\alpha = 1.0$ was calculated by considering one carboxylic acid moiety per monomeric unit with an equivalent weight of 194 g mol^{-1}. According to the modified Henderson-Hesselbach Equation, see Equation 5.20., pH was plotted against log $(\alpha/1-\alpha)$. The slope ie, n = 0.86 was then used to obtain a plot of pH against

Table 5.10 The Effect of Glucono-δ-Lactone Concentration on pH and Gelation of Calcium Alginate Gels. Ca^{2+} = 50 mM ; Alginate = 3.0 g dl^{-1} .

Concentration of Glucono-δ-Lactose (g dl^{-1})	pH	Gelation < 2 min
0.4	7.10	−
0.8	6.40	−
1.2	5.55	−
1.6	4.70	−
2.0	4.25	+
2.4	3.83	+
2.8	3.68	+
3.2	3.50	+
3.6	3.38	+
4.0	3.27	+

Table 5.11 The Effect of Alginate Concentration on pH and Gelation of Calcium Alginate Gels. Ca^{2+} = 50 mM ; Clucono-δ-Lactone = 2.0 g dl^{-1} .

Concentration of Alginate (g dl^{-1})	pH	Gelation < 2 min
0.59	3.13	+
1.01	3.30	+
2.10	3.50	+
3.05	3.74	+
4.22	3.94	+
4.96	4.07	+
6.06	4.23	+

Figure 5.8. The Effect of the Concentrations of Glucono-δ-Lactone, ●, and Alginate, ○, on the pH of Calcium Alginate Gels.
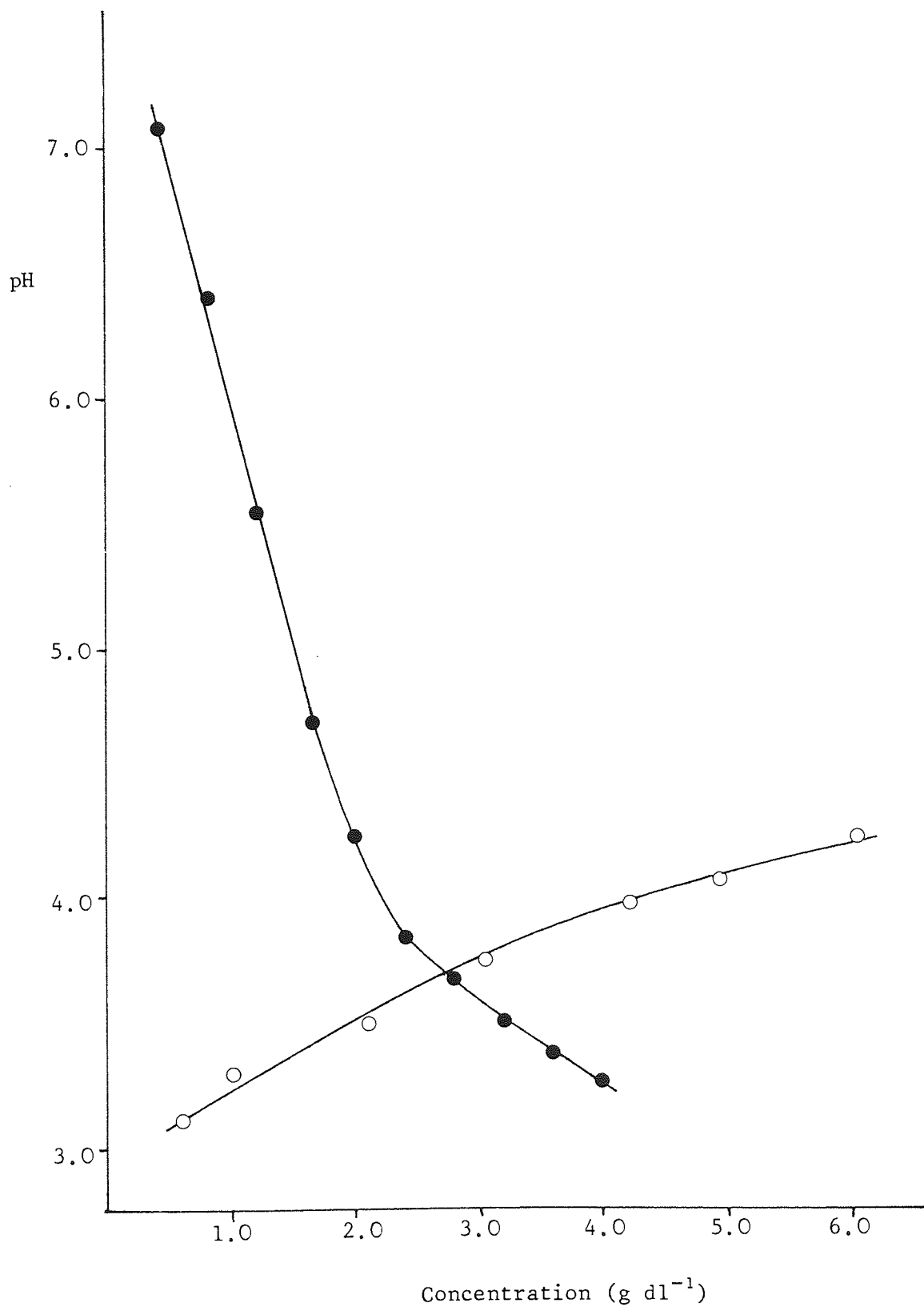
Table 5.12. Results for the Potentiometric Titration of Alginic Acid according to the method of Section 5.3.2.2..

Volume of 0.1 Na OH added (cm^3)*	Volume of 0.1 NaCl added (cm^3)*	pH	Degree of Neutralisation α	$\log\left(\dfrac{n\alpha}{1-n\alpha}\right)$
2.0	8.0	3.28	0.385	−0.306
3.0	7.0	3.61	0.577	0.007
4.0	6.0	3.83	0.769	0.290
4.2	5.8	4.05	0.808	0.358
4.4	5.6	4.09	0.846	0.428
4.6	5.4	4.18	0.885	0.503
4.8	5.2	4.35	0.923	0.586
5.0	5.0	4.71	0.962	0.679
5.2	4.8	6.53	1.000	0.788

* These volumes were added to individual 20 cm^2 aliquots

containing Alginic Acid 0.100 g.

$(n_\alpha /1 - n_\alpha)$ as given in Figure 5.9.. Bearing in mind that much of the titration was carried out with Alginic acid present in suspension, the plot shows reasonable linearity. The value of pKa was obtained from the ordinate when log $(n_\alpha /1 - n_\alpha)$ = 0, ie, pKa = 3.61.

By contrast, using the method advocated by Albert and Serjeant (253) by considering Alginic acid as a monoprotic acid with a molecular weight of 194 g mol^{-1} , a value of pKa = 3.33 $\pm$ 0.16 was obtained. This is in fair agreement with the value of 3.61 from the previous method. The wide standard deviation, however, probably results from using a two phase titration system.

From these results, it can be concluded that for gelation to occur by the GDL method, and to be independent of the presence of Alginic acid, the pH of the gel should be in the range 3.61 to 4.70. To achieve this, the concentration of GDL used subsequently was 2.0 g dl^{-1} and the relatively small effect of Alginate on pH enabled various concentrations to be used.

Figure 5.9.

DETERMINATION OF THE DISSOCIATION
CONSTANT FOR ALGINIC ACID USING THE
MODIFIED HENDERSON – HASSELBACH EQUATION
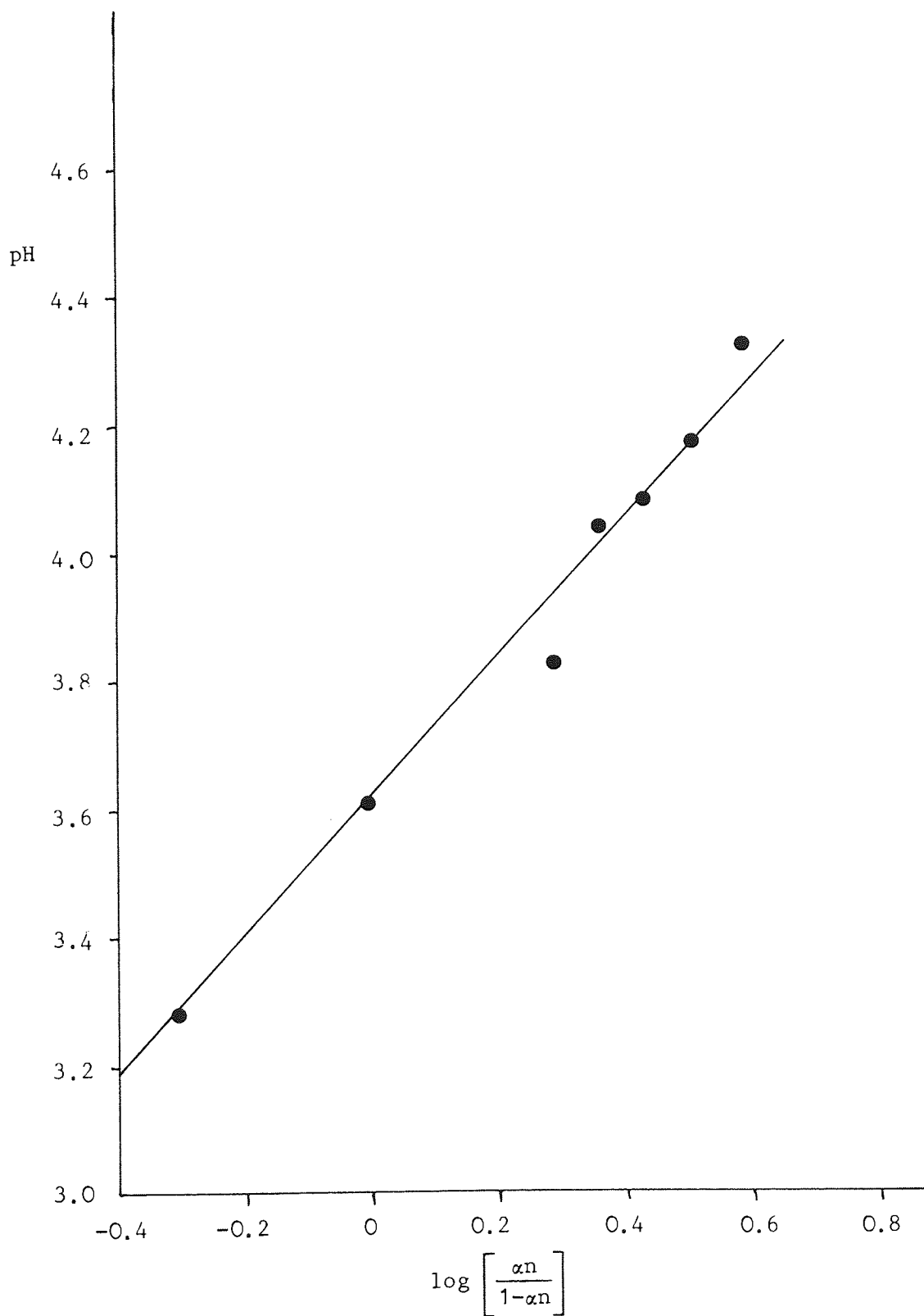
5.4.3.2 Effect of Calcium Ion Concentration on the Storage Modulus and Dynamic Viscosity.

The concentration range of 10 to 100 mmol Ca^{2+} was used for 3,0 g dl^{-1} Alginate gels measured using the oscillatory shear method given in Sections 2.3.4.2. and 5.3.2.2.. The distinct characteristic that arose from the results was that all of the gels, except the lowest Ca^{2+} concentration, showed purely elastic properties, ie, the phase angles were negligibly small. The dynamic viscosity curve, $\eta'(\omega)$, for 10mM Ca^{2+} is given in Figure 5.10. Here, the viscosity component changed dramatically whilst the storage modulus, G', remained virtually unchanged.

The plateau in the $G'(\omega)$ curve within the frequency range used was a consistent feature for all Calcium Alginate gels measured in this way. The collective results for $G'(\omega)$ are given in Table 5.13., and a specimen $G'(\omega)$ curve for 70 mMol Ca^{2+} is given in Figure 5.11. By calculating the mean value of G' from the plateau, representative values for the gel rigidity were obtained. These results are listed in Table 5.14. and illustrated in Figure 5.12.. It is clear that when the Ca^{2+} concentration was greater than 40 mMol, there was no significant increase in gel rigidity. This may be attributed to saturation of the available sites for Ca^{2+} cross-linking.

Figure 5.10. The Effect of the Frequency of Oscillation on the Storage Modulus G', $\bigcirc$, and the Dynamic Viscosity η', $\bullet$, of a Calcium Alginate Gel.

Alginate Concentration = 3.0 g dl^{-1}

Ca^{2+} Concentration = 10.0 mMol.
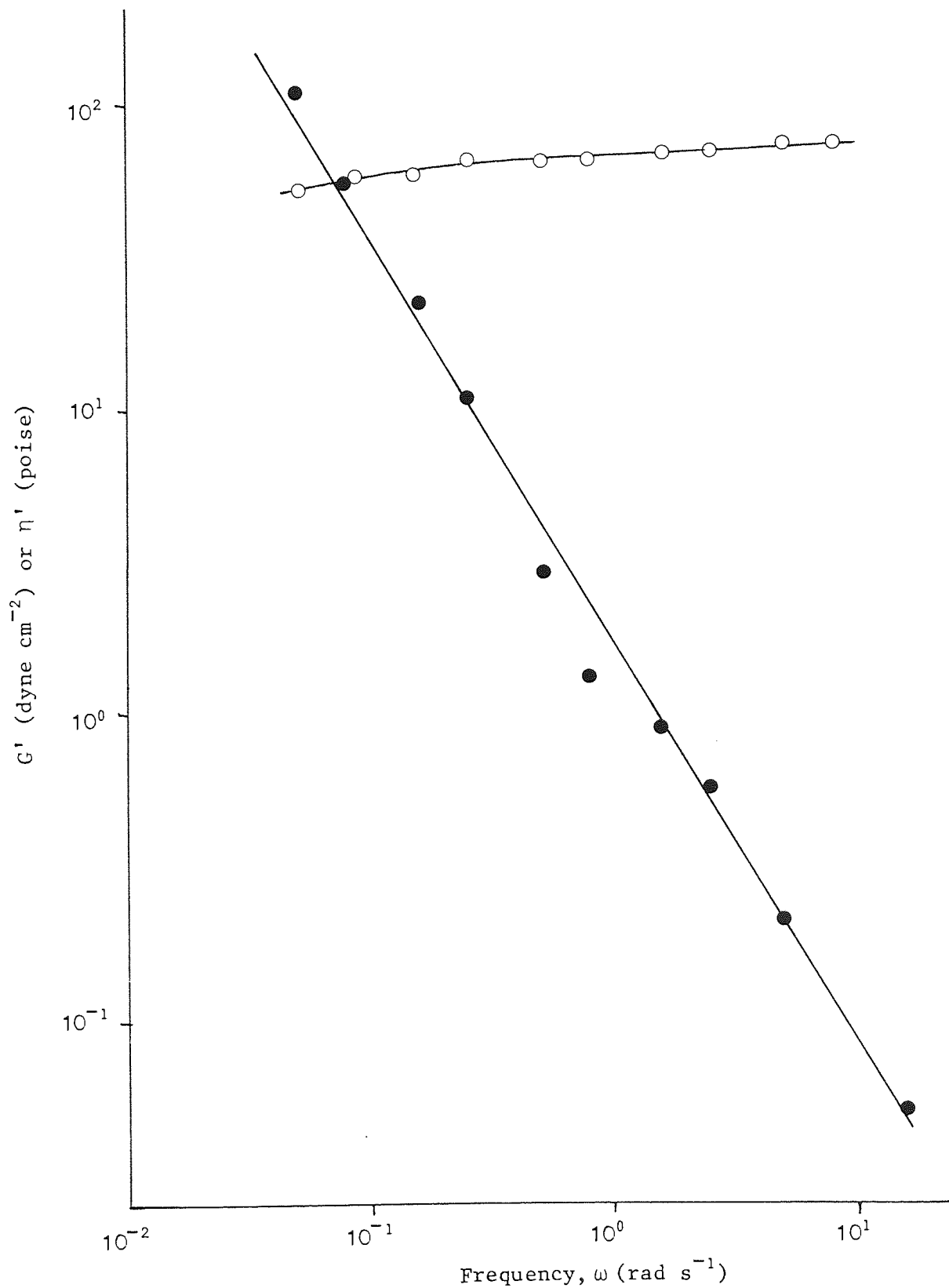
Table 5.13. Storage Modulus, $G(\omega)$, of 3.0 g dl^{-1} Alginate Gels as a function of the Calcium Ion Concentration.

Frequency (ω) (rad s^{-1})	Storage Modulus, G', (Dyne cm^{-2}) Calcium Ion Concentration (mMol.)							
	10	20	30	40	70	80	90	100
0.0497	54.04	2208	6270	7950	7423	5154	8402	5650
0.0792	56.69	3177	6152	8190	7063	6187	7586	8907
0.157	60.44	3065	5899	8982	7450	7120	6986	8953
0.249	67.64	3637	6094	8982	8771	7625	9231	8536
0.497	65.41	3664	6036	7711	7447	7306	8511	6903
0.792	68.21	3491	5965	7706	7462	7302	8070	8266
1.57	71.48	3443	7661	8375	7495	8560	9131	7592
2.49	72.17	3460	7131	6954	7711	8184	8282	7872
4.97	77.63	3472	6660	6214	7340	8120	7838	7478
7.92	76.62	3515	6843	6595	5444	8720	7576	6929
15.7	98.95	2820	5181	4512	3850	5460	5381	4787

Figure 5.11. The Effect of the Frequency of Oscillation on the Storage Modulus, G', of a Calcium Alginate Gel showing the Effect of the Natural Frequency, ω_o.

Alginate Concentration = 3.0 g dl^{-1}
Calcium Ion Concentration = 70 mMol
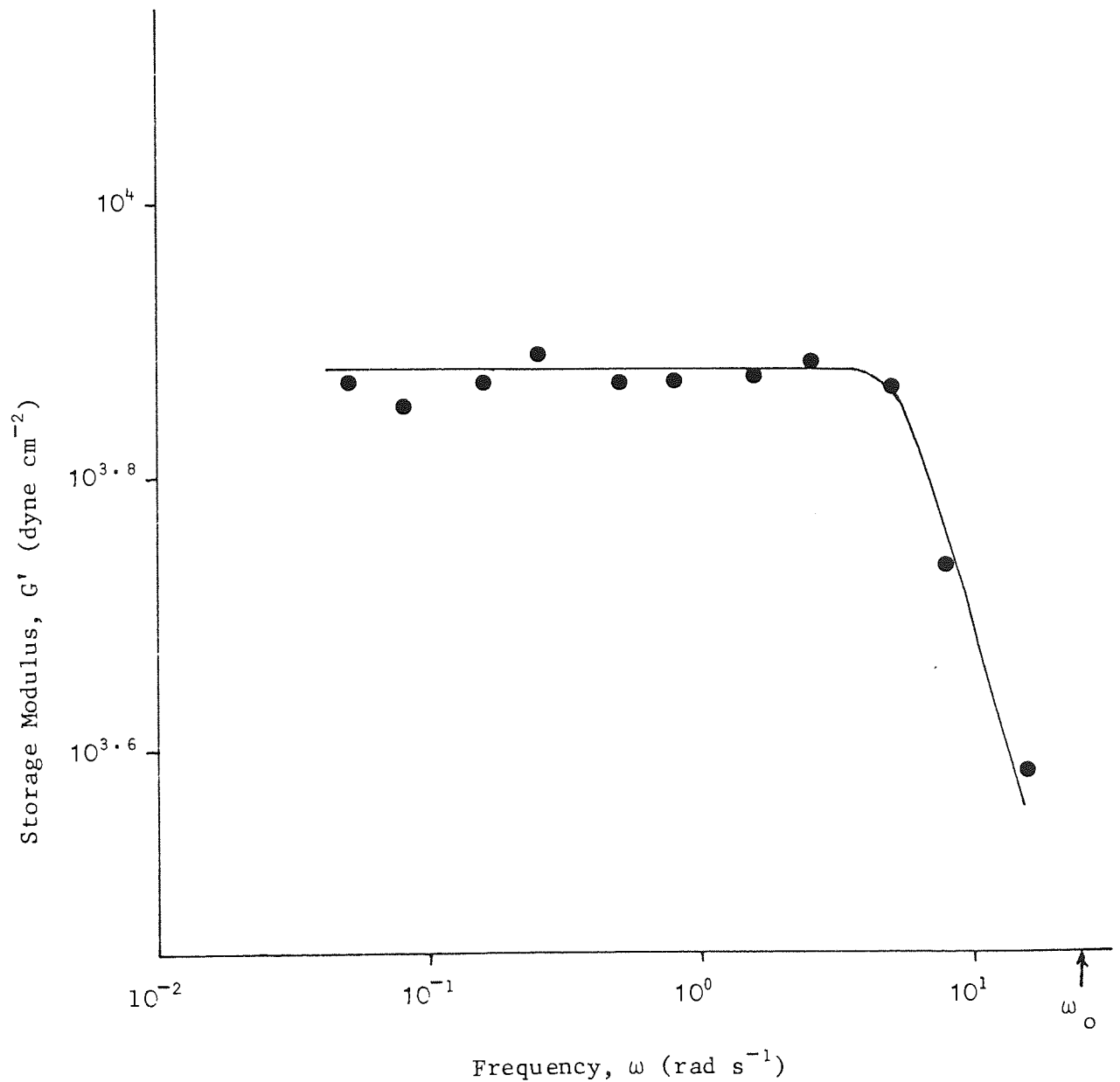
Table 5.14. Summary of the Results for Gel Rigidity, G',
as a function of Calcium Ion Concentration.

Ca^{2+} Concentration (mMol)	Mean G' from plateau of $G'(\omega)$ (dyne cm^{-2})	95% Confidence limits	Number of Readings
10	71.31	4.22	7
20	3436	151	9
30	6430	432	10
40	7766	786	8
70	7574	370	9
80	7867	511	8
90	8160	505	10
100	7937	600	9

Figure 5.12

THE EFFECT OF CALCIUM ION CONCENTRATION
ON THE STORAGE MODULUS, $G'(\omega)$, OF 3.0 g dl^{-1}
ALGINATE GELS
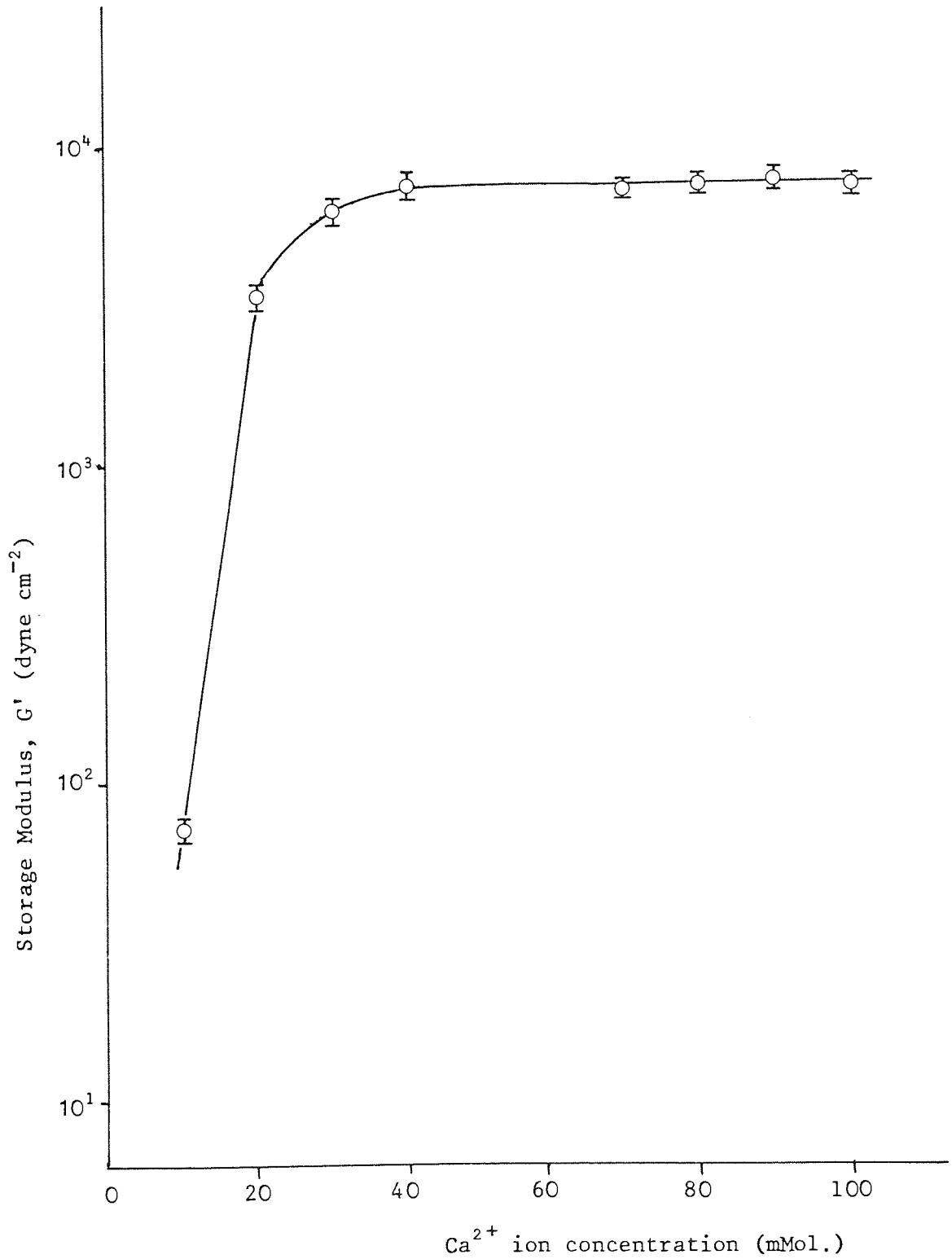
5.4.3.3 Effect of Alginate Concentration on the Storage Modulus.

The effect of Alginate concentration in the range 1.0 to 6.1 g dl^{-1} on gel rigidity as quantified by the storage modulus, $G'(\omega)$, was determined using the oscillatory shear method. The collective results for $G'(\omega)$ are given in Table 5.15.. The mean value of G' was obtained from the plateau of the $G'(\omega)$ curve as carried out in Section 5.4.3.2.. The resulting representative values are listed in Table 5.16. and illustrated graphically in Figure 5.13..

Within experimental error, the phase angles in oscillatory shear were zero for all gels and therefore they were purely elastic. The increase in G' with Alginate concentration was less marked than the increase in G' with Ca^{2+} concentration. This can be seen by comparison of Figures 5.10. and 5.11., remembering that the ordinate of the former bears a logarithmic scale. Data for concentrations of Alginate less than 1.0 g dl^{-1} was not available because the brittle nature of such gels prohibited their transfer, intact, to the parallel plate geometry of the rheogoniometer.

Usually, up to six Alginate gels had to be prepared by the Glucono-δ-lactone method in order to obtain one sample suitable for rheometry. There were two reasons for this. Firstly, some gels set rapidly after pouring giving a non-horizontal or non-flat upper surface.

Secondly, air occasionally became trapped in the gel as small bubbles: for low viscosity Alginate Solutions prior to

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Table 5.15. The Effect of Alginate Concentration on the Storage Modulus, G'(ω). of Calcium Alginate Gels containing 50 mMol. Ca^{2+}.

Frequency ω (rad s^{-1})	Storage Modulus, G' (Dyne cm^{-2}) Alginate Concentration (g dl^{-1})							
	1.0	1.5	2.1	2.7	3.1	4.2	5.0	6.1
0.0497	3900	3084	4353	5282	7706	6576	6942	7496
0.0792	3927	4345	5061	7895	6982	8284	6980	7791
0.157	4060	4742	5653	7656	7232	8695	8012	8623
0.249	4174	5471	5818	7842	8605	8546	7047	8502
0.497	4130	5543	7303	7412	7973	9280	7415	8462
1.792	3774	5158	7298	7753	8276	9348	7376	8150
1.57	3510	4794	7130	7517	8296	8355	8394	9217
2.49	3070	4708	7049	8012	8529	8463	7914	8934
4.97	3146	4211	6812	7940	8238	8010	9870	8700
7.92	4061	4394	6510	4980	8116	8106	8398	8156
15.7	2786	1535	3662	5171	6980	5708	5522	5776

Table 5.16. Summary of Results for the Effect of Alginate Concentration on the Storage Modulus, G', for Gels containing 50 mMol Ca^{2+}.

Alginate Concentration ($g\ dl^{-1}$)	Mean G' from plateau of $G'(\omega)$ ($dyne\ cm^{-2}$)	95% Confidence limits	Number of Readings
1.0	3735	291	10
1.5	5069	359	6
2.1	6697	542	8
2.7	7697	210	8
3.1	7941	350	10
4.2	8565	364	9
5.0	8053	735	8
6.1	8504	334	9

Figure 5.13.

THE EFFECT OF ALIGNATE CONCENTRATION ON THE
STORAGE MODULUS OF GELS CONTAINING 50 mM Ca^{2+}.

Storage Modulus, G' ($\times 10^3$ Dyne cm^{-2})

Alginate Concentration (g dl^{-1})
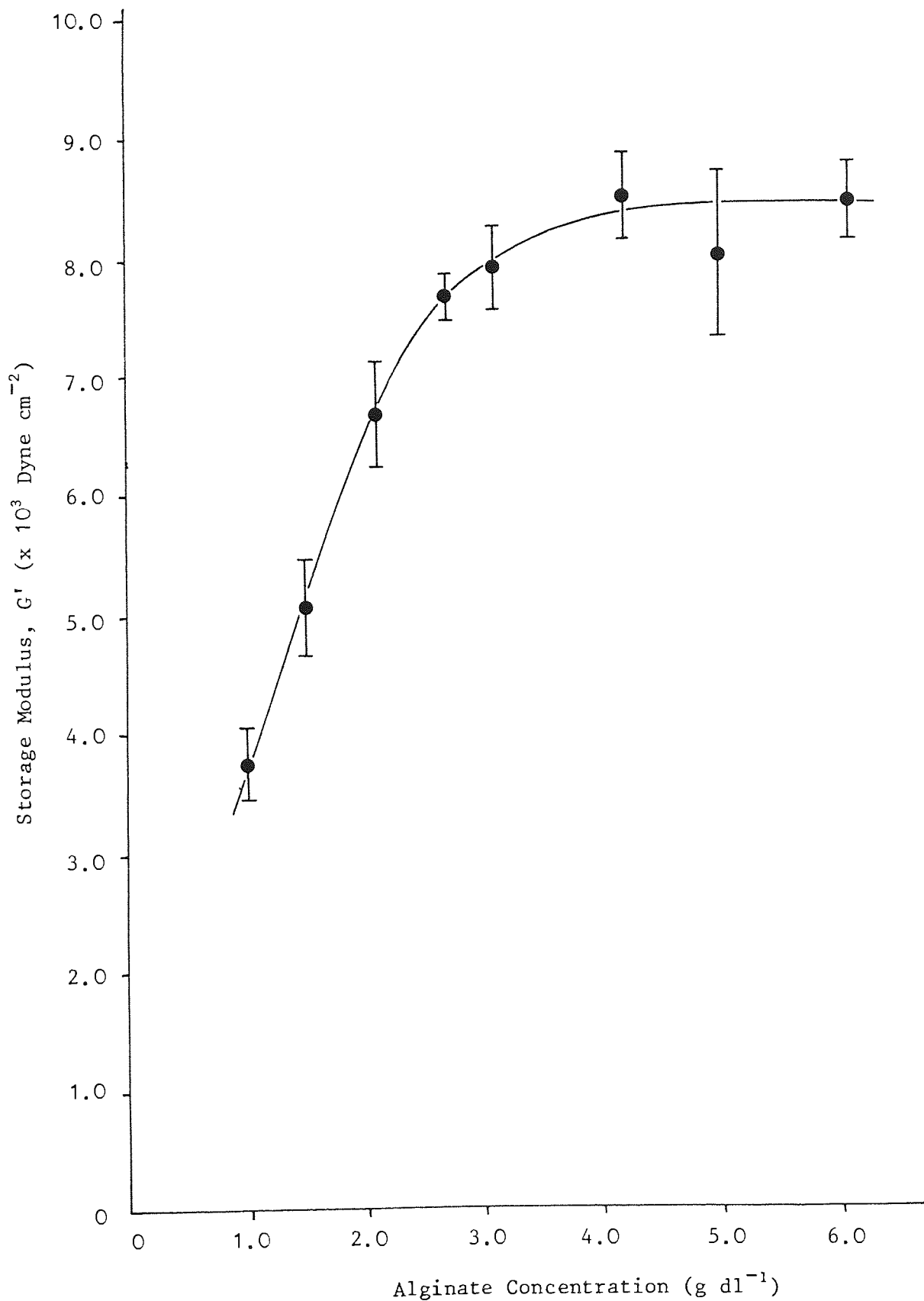
mixing with GDL, vigorous stirring was necessary to prevent sedimentation of the calcium salt. At higher viscosities, any air which became trapped was not liberated before gelation occurred.

5.5   Discussion

In Section 4.4., the results of numerical analysis showed that the plotting of diffusion data in a first order fashion gave good agreement. From this, it was concluded that without sound evidence of the mechanism of rate control, drug release profiles can be misinterpreted.

Consideration of experimental data provides an illustration of this. Table 5.17. lists the results of an experiment for the release of Ibuprofen from a Calcium Alginate gel in terms of the fraction released, F_e , against time. The experimental system is fully explained in Section 5.3.1.. From evidence given in earlier sections, the process was found to be diffusion controlled, and described by the planar diffusion equation described in Section 4.2.. By comparing the results of plotting F_e in a first order fashion with F_e against $\sqrt{t}$, then Figures 5.14(a) and (b) are obtained. The linear least mean square correlation coefficients are 0.9967 for the first order plot and 0.9996 for the $\sqrt{t}$ plot. Clearly, if a process known to be diffusion controlled gives such a high correlation in a first order plot then with more complex systems such as suspensions, creams and ointments, it is likely to be difficult to distinguish between a diffusion

Table 5.17.   Sample Set of Experimental Data for the Diffusion of Ibuprofen through a Calcium Alginate 5% Gel : the experimental method is give in Section 5.3.1.1. F_e is the Fraction Released at Time, t.

t(hr)	$\sqrt{t}$ (hr$^{\frac{1}{2}}$)	F_e	ln (1-F_e)
1	1.000	0.143	-0.154
2	1.414	0.210	-0.236
3	1.782	0.242	-0.277
5	2.236	0.311	-0.373
7	2.646	0.369	-0.460
10	3.162	0.434	-0.569
14	3.742	0.492	-0.677
25	5.000	0.647	-1.041
31	5.568	0.722	-1.280
43	6.557	0.845	-1.864

Figure 5.14

EXPERIMENTAL DATA FOR DRUG RELEASE BY
DIFFUSION : THE FRACTION RELEASED, F_e , PLOTTED
AS (a) $\sqrt{t}$ RELATIONSHIP AND (b) FIRST ORDER
RELATIONSHIP.

(a)

$$F_e = 0.124 \ t^{\frac{1}{2}} + 0.0304$$

(b)

$$\ln(1 - F_e) = 0.0381 \ t - 0.155$$

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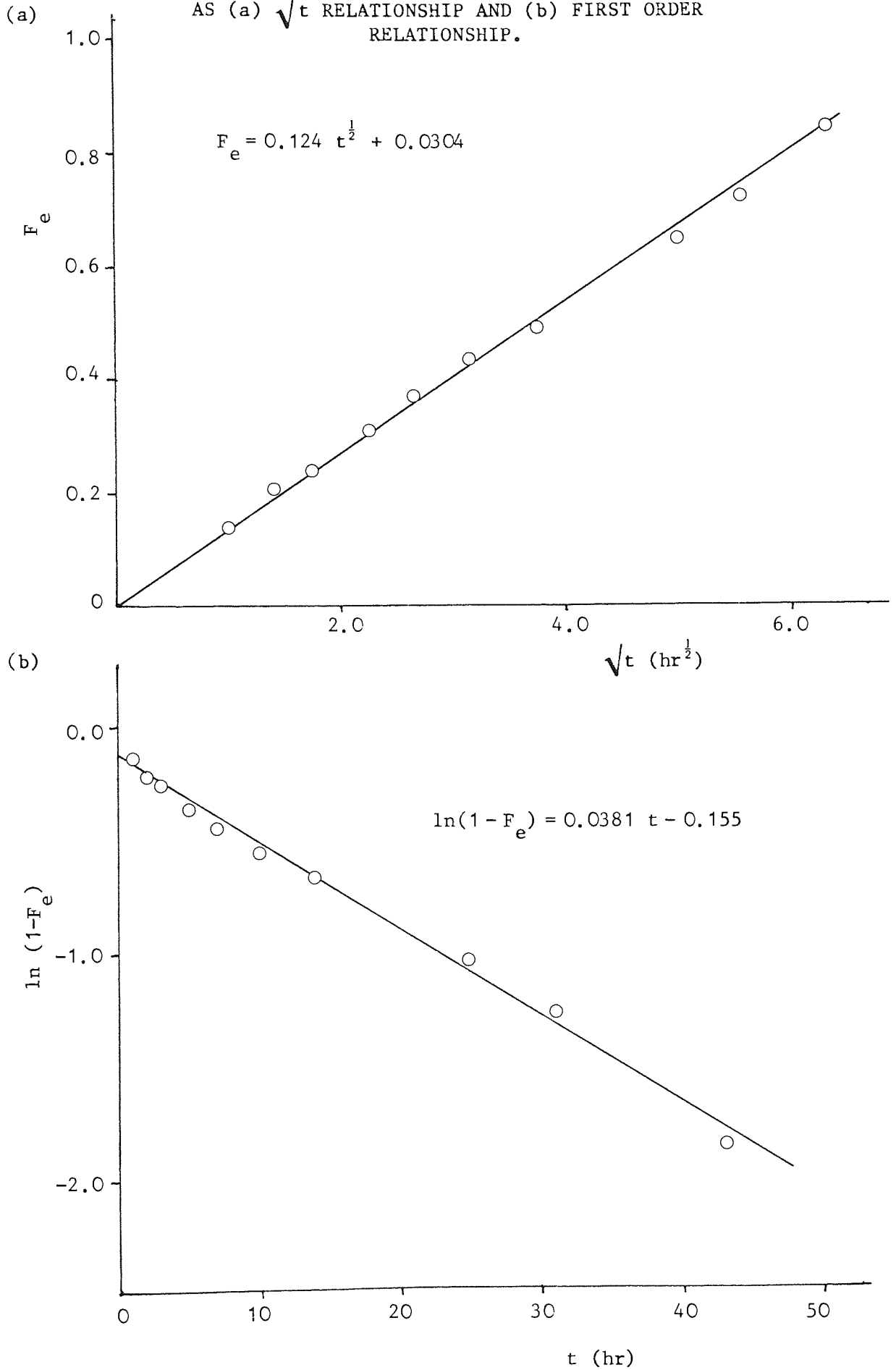
process and first order kinetics.

In Section 5.2.1., the calculation of the free diffusion coefficients of simple compounds was discussed. By calculating the free diffusion coefficient, D_f , of Ibuprofen in water at 25°C using Equations 5.7. and 5.8. derived from the Nernst-Einstein Equation 5.1., the values obtained can be compared with values of D the diffusion experiments in Section 5.4.2..

from

For the calculation, the molecular volume should be determined; this is approximated by the partial molal volume for which tabulated values are available (232, 254). The application to Ibuprofen in aqueous solution at a pH significantly above its pKa, is shown in Figure 5.15.. Substituting the resulting value of v = 183.4 $cm^3 mol^{-1}$ into Equations 5.7 and 5.8. for small and large molecules, we obtain D_1 = 8.71 x 10^{-6} and D_2 = 5.81 x 10^{-6} $cm^2 sec^{-1}$ respectively. In the case of the latter value, the molecule is assumed to be spherical and the frictional ratio, F = 1; corrections for non-sphericity usually account for less than a 10% change in F unless the molecule is highly elongated. By tabulating values of D_f for six homologous series of small molecules, Flynn (232) showed that species containing four or more carbon atoms gave experimental diffusivities within 25% of values calculated from Equation 5.8.. Albery et al (255) determined the values of D_f for the molecular weight carboxylic acids using a Stokes cell with a pH-Stat

Figure 5.15.   Partial Molal Volume of Ibuprofen from
                Substituent Values.

	Substituent	Partial Molal Volume (cm^3 mol^{-1})		Summation
	$-CH_3$	19.3	x 3	57.9
	$-H$	3.1	x 2	6.2
	$-COO^-$	11.5		11.5
	$-C-$	9.9	x 2	19.3
	$-C_6H_4-$	71.8		71.8
	$-CH_2-$	16.2		16.2

183.4

cm^3 mol^{-1}

Molecular Weight = 206.3 g mol^{-1}

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modification. They found that the theoretical D_f over-estimated the actual values by about 0.6×10^{-6} cm^2 sec^{-1} for oxalic and succinic acids. Therefore, the estimate of D_f for Ibuprofen, ie, either D_1, or D_2, may be greater than the true value.

In the experiments for diffusion of Ibuprofen through Alginate gels, it appeared that the values of D obtained were independent of the concentration of Alginate. If this was the case, then an overall value of D can be obtained from Table 5.8., ie, $\overline{D} = 4.82 \times 10^{-6}$ cm^2 sec^{-1} with 95% confidence limits of $\pm$ $0.228 \times 10^{-6} cm^2$ $sec^{-1}(N = 20)$. This value is lower than D_2 calculated from a theoretical approach. However, when an estimate of error of 25% for D_2 is taken into account, the lower limit is $D_2 = 4.36 \times 10^{-6} cm^2 sec^{-1}$; D_2 becomes insignificantly different from $\overline{D}$.

From this information, then according to the accuracy of the method for determining the theoretical D_f , then the diffusion coefficients of Ibuprofen in Calcium Alginate gels may not be significantly lower than the true value of D_f . To further investigate this aspect, there are several relationships available which equate D_f with values of D in gel matrices.

Lauffer (256) studied the theory of diffusion in gels and developed the equation:

$$D_g = D_f \frac{(1 - {}^5/3 \emptyset)}{(1 - \emptyset)} \qquad\qquad 5.21$$

where D_g = Diffusion coefficient in the gel.

$\emptyset$ = Volume fraction from which solvent is effectively excluded.

5/3 = Coefficient of obstruction for gels consisting of random rods.

Substituting $D = 5.81 \times 10^{-6} cm^2 sec^{-1}$ and $\emptyset = 0.05$ for a 5.0 g dl^{-1} Alginate gel, a value of $5.61 \times 10^{-6} cm^2 sec^{-1}$ is obtained. Before including estimates of errors, this is significantly higher than $\overline{D}$.

Another relationship was developed by Friedman and Kramer (223) to explain the diffusion of urea, sucrose and glycerol in gelatin gels:

$$D_f = D_g(1 + 2.4r_s/r_p) (1 + \alpha) (1 + \pi) \qquad 5.22$$

where α = viscosity correction factor obtained by comparing D_f with D_g extrapolated to zero gelatin concentration.

ie, $\alpha = \dfrac{D_f - D_{extrap.}}{D_f}$ \qquad 5.23

π = mechanical blocking constant due to Dumanski (257)

ie, $\pi = (g / d)^{2/3}$ \qquad 5.24

g = gelatin concentration

d = density of gel

$(1 + 2.4r_s / r_p)$ = Ladenberg's correction to Stokes' Law for the fall of spherical bodies in capillary tubes (258,259).

r_s = radius of solute diffusant molecule

r_p = radius of pores in the gel matrix.

Therefore, from a knowledge of r_s, α , π , D_g and D_f , the pore radius r_p can be calculated. If it is assumed that D_f

and D_g are 5.81×10^{-6} and 4.82×10^{-6} cm^2 sec^{-1}

respectively and putting $\alpha = 0$ by assuming the microscopic

viscosity remains unchanged, $g = 0.05$, $d = 1.0g$ cm^{-3},

$r_s = (3 \times 183.4/4\pi N_{AV})^{1/3}$, ie, $r_s = 4.17 \times 10^{-8}$ cm.

Therefore we obtain $r_p = 1.63 \times 10^{-6}$ cm which compares with

a mean of 0.53×10^{-6} cm determined by Friedman and Kramer

(223) for a 5.0 g dl^{-1} gelatin gel, with the inclusion of a

viscosity correction. Using Equation 5.22., Nixon and

coworkers (224) found it necessary to include an "aggregation

factor", X, to explain their data for diffusion of methylene

blue in gelatin-glycerol-water gels such that

$$D_f = D_g^{(1 + X)} (1 + 2.4\ r_s/r_p)\ (1 + \alpha)\ (1 + \pi) \qquad 5.25$$

where X approached unity when the dye molecules were not

aggregated.

When the concentration of gelling agent is sufficiently high

as to impede diffusion, the effect can be described in terms

of a reduction in the pore radius in the matrix such that free

diffusion no longer occurs. Therefore, the diffusivity in

small pores, D_p, will be less than D_f. The two

quantities have been equated by Renkin (260) in terms of the

equivalent solute radius and the cylindrical pore radius, r_s

and r_p respectively:

$$\frac{D_p}{D_f} = \left\{ 1 - \frac{r_s}{r_p} \right\}^2 \left[1 - 2.104 \left\{ \frac{r_s}{r_p} \right\} + 2.09 \left\{ \frac{r_s}{r_p} \right\}^3 - 0.95 \left\{ \frac{r_s}{r_p} \right\}^5 \right] \qquad 5.26$$

such that r_s/r_p approaches zero when D_p/D_f approaches

unity, and r_s approaches r_p when D_p approaches zero. The equation was developed to describe the diffusion of various molecules in cellulose membranes.

A useful approximation to Equation 5.26. exists when $r_s/r_p < 0.2$ (261) which was obtained empirically:

$$\frac{D_p}{D_f} = 1 - \left\{ \frac{r_s}{r_p} \right\}^4 \qquad\qquad 5.27$$

Using the information obtained from Equation 5.22. that $r_p = 1.63 \times 10^{-6}$ cm, then $r_s/r_p = 0.0256$ and from Equation 5.27., $D_p/D_f = 0.902$. Therefore, substituting $D_f = 5.81 \times 10^{-6}$ cm^2 sec^{-1}, we obtain $D_p = 5.24 \times 10^{-6}$ cm^2 sec^{-1}, which is in closer agreement with D_g for Ibuprofen in Alginate than the value of 5.61×10^{-6} from Equation 5.23. due to Lauffer (256).

From this calculation, it can be seen that because of the estimates of error of D_f and its possible over-estimation for carboxylic acids (255), then it is difficult to discern whether the diffusion coefficient of Ibuprofen in various Calcium Alginate gels is significantly different from D_f. In addition, the nature of the dialysis gel formation method meant that a range of Calcium ion concentrations could not be used: unsaturated Ca^{2+} binding was found to give rise to a Ca^{2+} concentration gradient in the gel.

However, with increasing Alginate concentration, the diffusion coefficient of Ibuprofen appeared to remain

unchanged despite an increase in the gel rigidity as measured by the Storage Modulus, G'. Therefore, the reduction in pore radius which inevitably resulted from increasing the Alginate concentration was insufficient to retard the diffusion of a molecule of the size of Ibuprofen. It is possible that a further increase in Alginate concentration or the use of a larger diffusant may produce a more marked effect.

6.   CONCLUSION

In this thesis, several different experimental techniques have been used to quantitatively describe the functions of Alginate in pharmaceutical systems.

Studies on the molecular properties of Alginate using viscometry and light scattering were carried out in order to obtain estimates of molecular weight, radius of gyration, second virial coefficient and statistical segment length. Centrifugation at 100,000 x g was necessary to clarify Alginate solutions for light scattering. The results showed good agreement with similar parameters obtained in previous studies. Continuous and oscillatory shear rheometry were used to describe the flow properties of Alginate solutions in terms of the non-Newtonian behaviour and the viscous and elastic components. The onset of non-Newtonian behaviour with increasing Alginate concentration was coincidental with the appearance of a significant elastic component.

By blending Alginate with other polyelectrolyte suspending agents namely Xanthan gum and 'Carbopol', it was found that a very wide range of rheological 'profiles' existed. From the use of such a wide range of properties, the formulation of pharmaceutical disperse systems is rationalised because of reduced dependence upon the rheological characteristics of the limited number of commercially available suspending agents. The use of oscillatory shear testing can describe a non-Newtonian suspending agent solution in terms of the viscous and elastic components. It has been shown here that this technique is particularly suited to the description of the rheological 'profiles' of suspending agent blends.

Many of the problems of dispersion rheology in pharmaceuticals
are common to other industries. For example, the prevention of
sedimentation during storage is important in liquid abrasive
cleaners, paints and printing inks as well as drug suspensions
(139). Because of the variable properties of the drugs which
must be suspended, it would not be possible to derive a single
desirable rheological 'profile' for all drug suspensions. Never-
theless, it appears that relatively little research has been
carried out in pharmaceutical institutions into the rheological
parameters important in suspension formulation.

In addition, other industries such as the food and paper industries
have found that by using microprocessor based controllers, fewer
batches of product are wasted from failure to comply with
rheological standards. It is likely that closer attention to
rheological properties in pharmaceuticals will yield a higher
quality product at a lower final cost.

It has been known for many years that the diffusion of a solute is
affected by the viscosity of the medium. However, an inverse
proportionality relationship is frequently inadequate to describe
the diffusion and for non-Newtonian media such as gels, quantifying
the viscosity becomes a problem in itself. In the literature,
studies on the diffusion of solutes in viscous and non-Newtonian
media have only rarely used a non-empirical rheological approach.
Consequently, little work has emerged concerning the effect of
viscoelasticity on diffusion.

In this study, diffusional and oscillatory shear rheological
techniques have been used for Calcium Alginate systems. Numerical
analysis showed that calculations from drug release profiles alone

do not demonstrate the presence of a diffusion mechanism, therefore further evidence for diffusion is essential. The diffusion mechanism was fully characterised for Ibuprofen as solute in Calcium Alginate gels. The elastic moduli from oscillatory testing, varied by changes in Alginate and Calcium ion concentrations, was found to have little or no significant effect on the diffusion coefficient. This was attributed to the fact that the pore size within the gel matrix remained significantly greater than the diameter of the diffusant molecule. There is much scope for future work in this field to discern more precisely, the relationship between diffusion and viscoelasticity.

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APPENDIX II   GLOSSARY OF TRADITIONAL AND SI UNITS

Throughout the text of this thesis a consistent system of units has been used for molecular, rheological and diffusional parameters such that the numbers produced were not cumbersome. However, the units were not necessarily in accordance with the SI convention. The Table below provides a list of the 'traditional' units used and their conversion to the SI system.

Measurement	Traditional Units	SI Equivalent
Viscosity	Poise	10^{-1}Nsm^{-2} (or Pas)
Force	Dyne	10^{-1} N
Shear Stress	Dyne cm^{-2}	10^{-1} Nm^{-2} (or Pa)
Volume	dl	10^{-4}m^3
Volume	cm^3	10^{-6} m^3
Weights	g	10^{-3} kg.

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