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PROCYANIDIN GELS BASED ON CELLULOSE AND CARRAGHENAN DERIVATIVES

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ABSTRACT

The formulation of procyanidin gels based on cellulose and carraghenan derivatives was studied. These gels need to have pH values compatible with anti-ulcer therapy, and a satisfactory viscosity. Their consistency was evaluated by measuring their spreading diameter, and by a rheological study. The speading diameter and viscosity of the formulations based on cellulose derivatives were linearly related.

INTRODUCTION

In previous work, we prepared procyanidins by fermentation of an extract of *Fragaria vesca* (1-4). We studied their use as raw materials for making active complexes (5, 6). These procyanidins also proved to possess angioprotector properties and marked anti-ulcer properties in Rat (7, 8). We went on to develop direct compression tablet forms (9), and effervescent dosage forms that are particularly appropriate for anti-ulcer therapy (10-13).

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The first results from procyanidin gel dosage forms, a form often used to administer antacids, have recently been published (14). The work reported here concerns the preparation and the compared rheology of gel formulations based on cellulose derivatives and on carraghenans.

Cellulose derivatives are widely used for dosage forms and afford limpid hydrogels with pH values suitable for anti-ulcer therapy (15). Carraghenans are colloids used extensively in food processing and cosmetics and pharmaceutical manufacturing,in particular as gelling agents (16). In addition, they possess a marked antipepsin activity, making them appropriate for procyanidin gel formulations.

MATERIAL AND METHODS

Raw Materials

The following cellulose derivatives were tested as gelling agents. Methylcellulose : Benecel MC 4000 PS®, Benecel M 142 C® (Aqualon) ; hydroxypropylcellulose : Klucel M®, Klucel H® (Aqualon) ; methylhydroxypropylcellulose : Benecel MP 324 C®, Benecel MP 363 C®, Benecel MHPC 4000 PS® (Aqualon).

The following carraghenans were tested. Aubygum X_2®, Aubygel X 52®, Satiagel HV®, Satiagum Standard® (Sanofi Bio-Industries).

The procyanidins incorporated into the gels were prepared by us (1).

Methods

Preparation of Gels

Cellulose derivatives : the gelling agent was dispersed in water with an IKA RW20 helical stirrer, at 35°C for formulations 1, 5, 9, 13, 17, 21, 25, 29, at 20°C for formulations 2, 6, 10, 14, 18, 22, 26, 30, 39-43, at 10°C for formulations 3, 7, 11, 15, 19, 23, 27, 31, 33 - 38, 44-56 and at 6°C for formulations 4, 8, 12, 16, 20, 24, 28, 32. The stirring rate was set at 500 r.p.m. ; the dispersion of 600 g of gel took 15 minutes.

Carraghenans : the gelling agent was dispersed in water with an IKA RW 20 helical stirrer at 35°C ; after dispersion the solution was warmed at 50°C for 5 min. The stirring rate was set at 500 r.p.m.; the dispersion of 600 g of gel took 20 minutes.

Determination of Spreadability

One gram of gel 24 hours old was pressed between two horizontal plates 20 cm square, of which the upper one weighed 125 g, and its diameter was measured against time (14).

Rheological Study

A rheological study of the gels was carried out at 21°C using a Brookfield RVTD V_2® instrument fitted with an SC_4-28/13 R Small Adapter.

RESULTS AND DISCUSSION

Gels based on cellulose derivatives

56 gels were prepared, containing 1 % procyanidins and 0.15 % Nipagine®, and a range of concentrations of gelling agent.

Four types of cellulose derivatives were tested ; methylcelluloses, hydroxypropylcelluloses, methylhydroxyethylcelluloses and methylhydroxypropylcelluloses. These cellulose ethers, Klucel® and Benecel®, are used in the preparation of hydrogels in the food and pharmaceutical industries (15).

Influence of dispersion temperature

The technical literature for the cellulose ethers Klucel® and Benecel® (15) indicates that two parameters influence gel consistency.

(i) The stirring rate during dispersion. For a given concentration of the cellulose derivative, the higher the stirring rate, the faster the gelling.

(ii) The dispersion temperature. The viscosity of the final gel decreases as the temperature of dispersion increases ; flocculation even occurs at temperatures above 50°C.

Preliminary trials showed that a stirring rate of 500 r.p.m. afforded rapid gelling (15 min.) without excessive inclusion of

TABLE 1

Gels based on Cellulose Derivatives. Influence of Dispersion Temperature on Gel Consistency

Cellulose derivative	Gelling agent	Concentration % (w/w)	Dispersion temperature (°C)	Spreading diameter after 1 min (mm)	Formulation n°
Methylcellulose	Benecel MC 4000 PS®	1	35	122.5	1
			20	114	2
			10	109.5	3
			6	108.5	4
	Benecel M 142 C®	3	35	79	5
			20	76	6
			10	72	7
			6	71.5	8
Hydroxypropyl cellulose	Klucel M®	1.5	35	79.5	9
			20	65.5	10
			10	65	11
			6	65	12
	Klucel H®	1	35	92	13
			20	71.5	14
			10	71.5	15
			6	71	16
Methyl hydroxyethyl cellulose	Benecel ME 233 P®	2	35	78.5	17
			20	74	18
			10	72	19
			6	71.5	20
Methyl hydroxypropyl cellulose	Benecel MP 324 C®	1	35	78	21
			20	74	22
			10	72	23
			6	72	24
	Benecel MP 363 C®	1	35	97	25
			20	94	26
			10	92	27
			6	91.5	28
	Benecel MHPC 4000 PS®	1	35	110	29
			20	105	30
			10	103.5	31
			6	103	32

air bubbles. The optimal dispersion temperature was determined by comparing the spreading ability of hydrogels prepared à 35°C, 20°C, 10°C and 6°C. The spreading diameter reached after one minute is a good measure of consistency. Under the experimental conditions reported elsewhere (14), the following classification was adopted: semi-stiff gels $\emptyset \leqslant 50$ mm ; semi-fluid gels $50 < \emptyset < 70$ mm and fluid gels $\emptyset \geqslant 70$ mm.

Table 1 clearly shows the influence of temperature on gelling with Benecel® and indicates a temperature of 10°C as a suitable temperature for dispersion ; the lower temperature of 6°C only slightly modified the consistency of the gel. At 35°C, gelling with Klucel® was impaired, but the consistencies of the gels obtained at 20, 10 and 6°C was satisfactory regardless of the temperature. Accordingly we chose 20°C for subsequent formulations. Table 1 also shows that all the gels prepared were fluid (Ø > 70 mm) except for those based on Klucel M®. As most of the antacid gels currently on the market (17) are semi-fluid, the concentrations of gelling agent needs to be increased.

The following formulations were compared using three main criteria (14) : (i) pH, which must be appropriate for anti-ulcer therapy, (ii) spreading diameter, which must be tetween 50 to 70 mm and (iii) rheological behaviour.

pH and spreading diameter

As can be seen in Table 2, all the gels prepared had suitable pH values, between 9.0 and 9.4.

Measurement of spreading diameter of the gels after one minute shows that most of them were semi-fluid, except for formulations n°s 35, 45, 46, 49 and 53, which were discarded.

Table 2 also shows that the results are reproducible. We went on to study the theological behaviour of those formulations that were found satisfactory, and to determine whether there was any correlation betxeen spreading diameter and viscosity.

Rheological Study

The rheological study of the gels showed them to be pseudoplastic and non-thixotropic. This is illustrated by the rheograms obtained with formulations 33, 40, 44 and 50 (Figure 1).

Relationship between spreading diameter and viscosity

Gel viscosity at 10 r.p.m. ranges from 1750 m.Pa.s. for formulation 39 to 10610 m.Pa.s. for formulation 43, (Table 3) which

TABLE 2

pH and Spreading Diameter of Gels based on Cellulose Derivatives

Formulation n°	Gelling agent	Concentration % (w/w)	pH	Spreading diameter after 1 min (mm)	
				$\bar{M}$ (3 measurements)	Δm
33	Benecel MC 4000 PS	2.5	9.2	60	0.0
34	Benecel MC 4000 PS	3	9.4	55	0.0
35	Benecel MC 4000 PS	3.5	9.3	49.5	0.5
36	Benecel M 142 C	4	9.5	61.5	0.0
37	Benecel M 142 C	4.5	9.35	54.5	0.5
38	Benecel M 142 C	5	9.3	51.5	0.5
39	Klucel M	1.5	9.4	63	0.0
40	Klucel M	2	9.4	58.5	0.5
41	Klucel M	2.5	9.4	53	0.0
42	Klucel H	1.5	9.3	59	0.5
43	Klucel H	2	9.5	50.5	0.5
44	Benecel ME 233 P	3	9.0	54	0.0
45	Benecel ME 233 P	3.5	9.2	50	0.0
46	Benecel ME 233 P	4	9.2	45	0.0
47	Benecel MP 324 C	1.5	9.4	60.5	0.5
48	Benecel MP 324 C	2	9.35	54	0.0
49	Benecel MP 324 C	2.5	9.4	46	0.0
50	Benecel MP 363 C	2	9.3	62	0.5
51	Benecel MP 363 C	2.5	9.4	56	0.0
52	Benecel MP 363 C	3	9.35	53	0.0
53	Benecel MHPC 4000 PS	2	9.4	70.5	0.5
54	Benecel MHPC 4000 PS	2.5	9.35	60.5	0.5
55	Benecel MHPC 4000 PS	3	9.35	54.5	0.5
56	Benecel MHPC 4000 PS	3.5	9.4	52.5	0.5

corresponds to spreading diameters of respectively 63 and 50.5 mm ; spreading diameter and viscosity are linearly related (Figure 2).

Gels based on carraghenans

37 gels were prepared, containing 1 % procyanidins, 0.15 % Nipagine® and a range of concentrations of gelling agent.

Four types of carraghenans were tested : Aubygum X_2®, Aubygel X_{52}®, Satiagum Standard® and Satiagel Standard® . The gelling power of these colloids depends on the dispersion temperature (set at 35°C), and the colloid concentration, and also on the presence of certain dissolved cations (16) ; we therefore studied the influence of sodium ion on the rheological behaviour of the gels.

The various formulations were compared according to the same three criteria as above, (i) pH, (ii) spreading diameter and (iii) rheological behaviour.

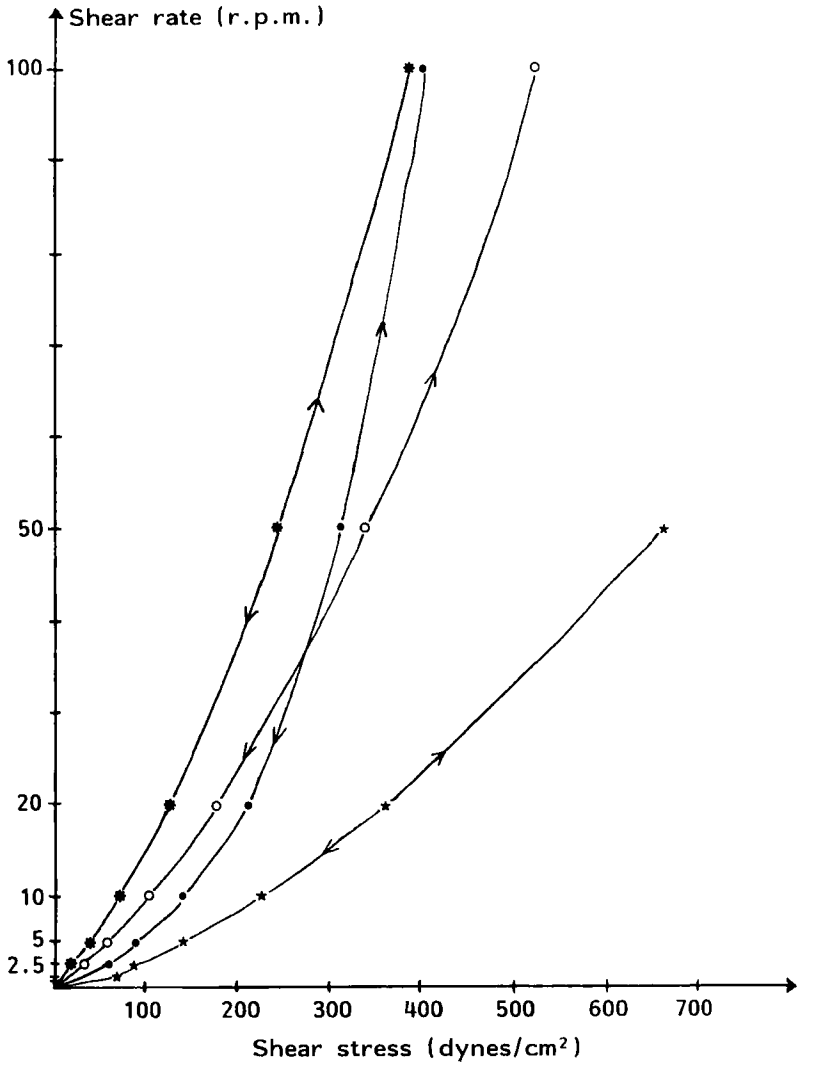

FIGURE 1

Gels based on cellulose derivatives. Exemples of rheograms Formulation 33 :o Benecel MC 4000 PS 2.5 % (MC) ; • Formulation 40 : Klucel M 2 % (HPC) ; ⋆ Formulation 44 : Benecel MC 233 P 3 % (MHEC) ; ✱ Formulation 50 : Benecel MP 363 C 2 % (MHPC)

TABLE 3

Viscosity at 10 r.p.m. of Gels based on Cellulose Derivatives.

Formulation n°	33	34	36	37	38	39	40	41	42	43	44	47	48	50	51	52	54	55	56
η at 10 r.p.m. (m.Pa.s)	3680	7260	2720	7540	9810	1750	4860	8805	4740	10610	7940	3300	8040	2520	6645	8710	3300	7850	9080

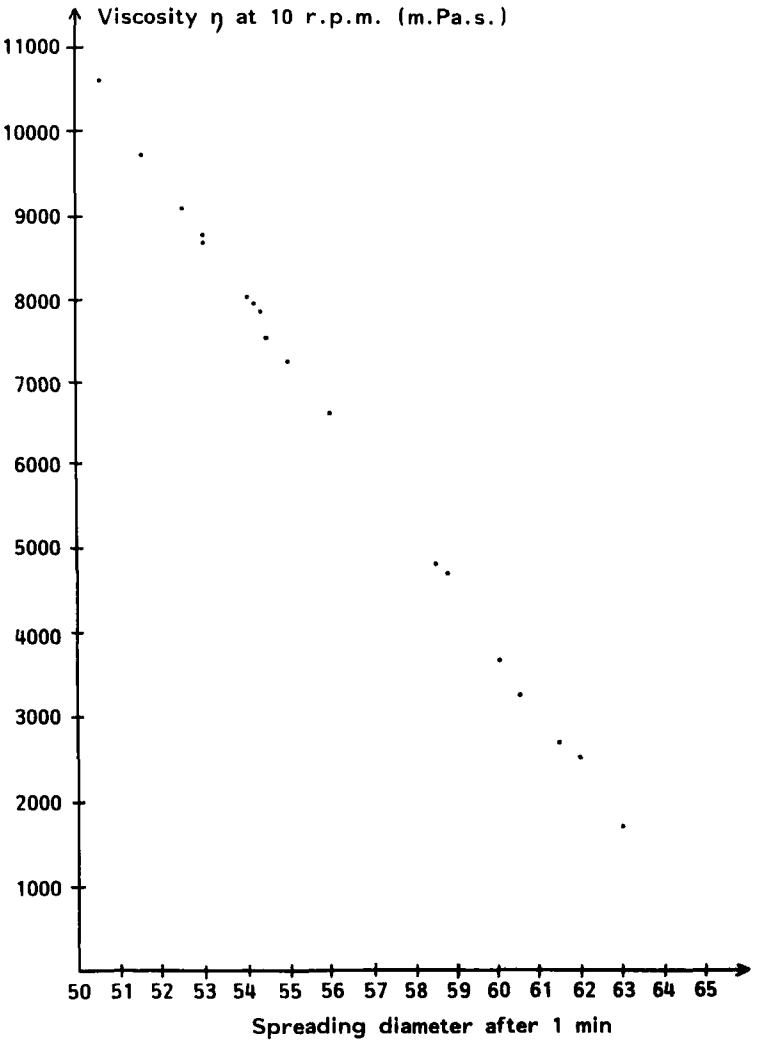

FIGURE 2

Gels based on cellulose derivatives.

Relationship between viscosity and spreading diameter.

TABLE 4

pH and Spreading Diameter of Gels based on Carraghenans

Formulation n°	Gelling agent	% (w/w) Gelling Agent	NaCl % (w/w)	pH	Spreading diameter after 1 min (mm)	
					$\bar{M}$ (3 measurements)	Δm
57	Aubygum X_2	2	-	9.15	89	1.0
58	Aubygum X_2	2.3	-	9.2	64	0.5
59	Aubygum X_2	2.4	-	9.3	61.5	0.5
60	Aubygum X_2	2.5	-	9.3	56	0.5
61	Aubygum X_2	2.8	-	9.4	48	0.5
62	Aubygum X_2	1.3	0.65	8.9	79	1.0
63	Aubygum X_2	1.5	0.75	8.9	65.5	1.0
64	Aubygum X_2	1.7	0.85	8.9	60	1.0
65	Aubygum X_2	1.8	0.9	8.9	55	1.0
66	Aubygum X_2	2	1	8.9	43	1.0
67	Aubygel X_{52}	1	-	9.5	108	1.0
68	Aubygel X_{52}	1.25	-	10.3	77	1.0
69	Aubygel X_{52}	1.5	-	9.5	56.5	0.5
70	Aubygel X_{52}	1.75	-	9.55	51	0.5
71	Aubygel X_{52}	2	-	9.5	47	0.5
72	Aubygel X_{52}	1	0.5	8.4	78	1.0
73	Aubygel X_{52}	1.3	0.65	8.4	68.5	1.0
74	Aubygel X_{52}	1.4	0.7	8.4	52.5	1.0
75	Aubygel X_{52}	1.5	0.75	8.4	49	1.0
76	Aubygel X_{52}	1.6	0.8	8.5	47.5	1.0
77	Satiagum Standard	2	-	10	72.5	1.0
78	Satiagum Standard	2.5	-	10.1	63.5	0.5
79	Satiagum Standard	3	-	10.2	57	0.5
80	Satiagum Standard	3.5	-	10.1	50	0.5
81	Satiagum Standard	1.5	0.75	9.6	82	1.0
82	Satiagum Standard	2	1	10.1	68	1.0
83	Satiagum Standard	2.5	1.25	9.6	58	1.0
84	Satiagum Standard	3	1.5	9.5	46	1.0
85	Satiagel Standard	2	-	9.9	72.5	1.0
86	Satiagel Standard	2.5	-	10.1	67.5	0.5
87	Satiagel Standard	3	-	10	61	0.5
88	Satiagel Standard	3.5	-	10.1	57.5	0.5
89	Satiagel Standard	4	-	10.1	46.5	0.5
90	Satiagel Standard	2	1	9.8	70	1.0
91	Satiagel Standard	2.5	1.25	9.7	57	1.0
92	Satiagel Standard	3	1.5	9.8	57.5	1.0
93	Satiagel Standard	3.5	1.75	9.7	50	1.0

pH and spreading diameter

All the gels prepared had pH values between 8.4 and 10.3, compatible therefore with anti-ulcer therapy (Table 4).

Measurements of spreading diameter allowed us to eliminate gels that were either too stiff (formulations 61, 66, 71, 76, 84, 89, 93) or too fluid (formulations 57, 62, 67, 68, 72, 77, 81, 85). In addition, it was found that for a given concentration of gelling agent, the presence of sodium ion afforded stiffer gels, par-

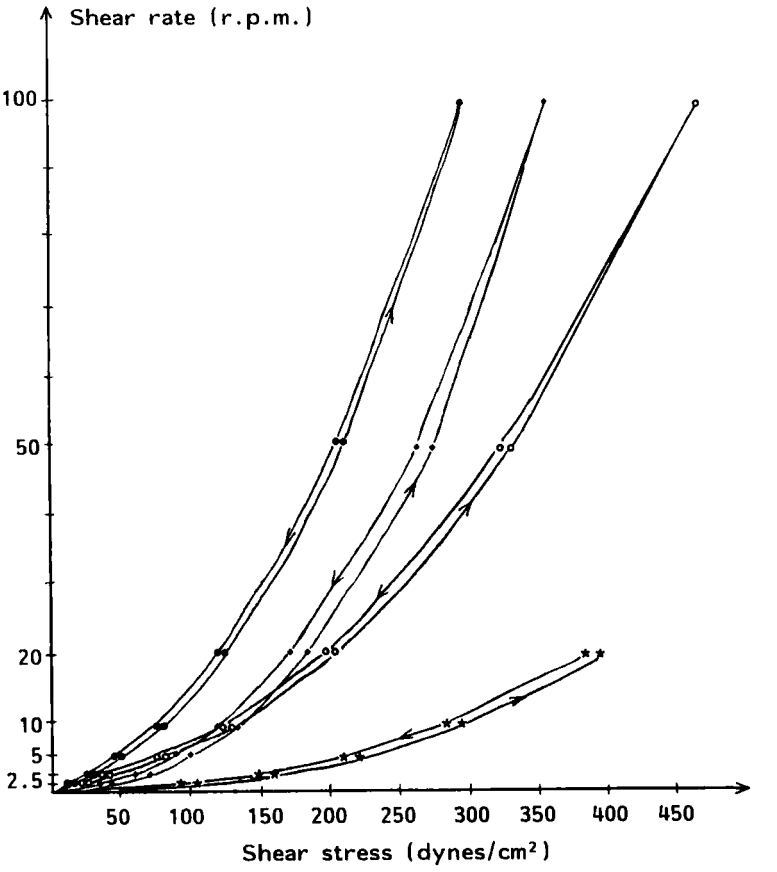

FIGURE 3

Gels based on carraghenans. Exemples of rheograms

Formulation 78 :• Satiagum standard 2.5 % ; • Formulation 83 : Satiagum standard 2.5 % - NaCl 1.25 % ; o Formulation 88 : Satiagel standard 3.5 % ; * Formulation 93 : Satiagel standard 3.5 % - NaCl 1.75 %

ticularly with Aubygum X_2® (formulations 57 and 66), though these gels seemed brittler.

Table 4 also shows the reproductibility of the results to be satisfactory overall though less so for gels containing carraghenans and NaCl.

TABLE 5

Viscosity at 10 r.p.m. of Gels based on Carraghenans

Formulation n°	58	59	60	63	64	65	69	70	73	74	78
η at 10 r.p.m. (m.Pa.s)	2340	4920	3520	2500	2880	4100	8320	7160	4400	12000	2900

Formulation n°	79	80	82	83	86	87	88	90	91	92	93
η at 10 r.p.m. (m.Pa.s)	5040	10900	2000	4720	1540	3620	4540	2020	5760	4840	10200

The rheological behaviour of the formulations that were retained was then studied, and the spreading diameter/viscosity relationship was plotted.

Rheological Study

The rheological study of the gels showed them to be pseudoplastic and thixotropic. Examples of rheograms obtained with formulations 78, 83, 88 and 93 (figure 3) show the influence of sodium ion on the consistency of the gels, the formulations containing carraghenans and NaCl are more viscous and more thixotropic.

Relationship between spreading diameter and viscosity

The viscosities of the gels at 10 r.p.m. (Table 5) ranged from 1540 m.Pa.s. for formulation 86 to 12000 m.Pa.s. for formulation 74, corresponding to spreading diameters of respectively 67.5 and 52.5 mm. However, unlike the cellulose-based gels, those based on carraghenans showed no tight linear relationship between spreading diameter and viscosity (figure 4) ; this can be accounted for by their thixotropic nature.

CONCLUSION

We prepared a series of procyanidin gels with pH values compatible with anti-ulcer therapy and satisfactory consistency as

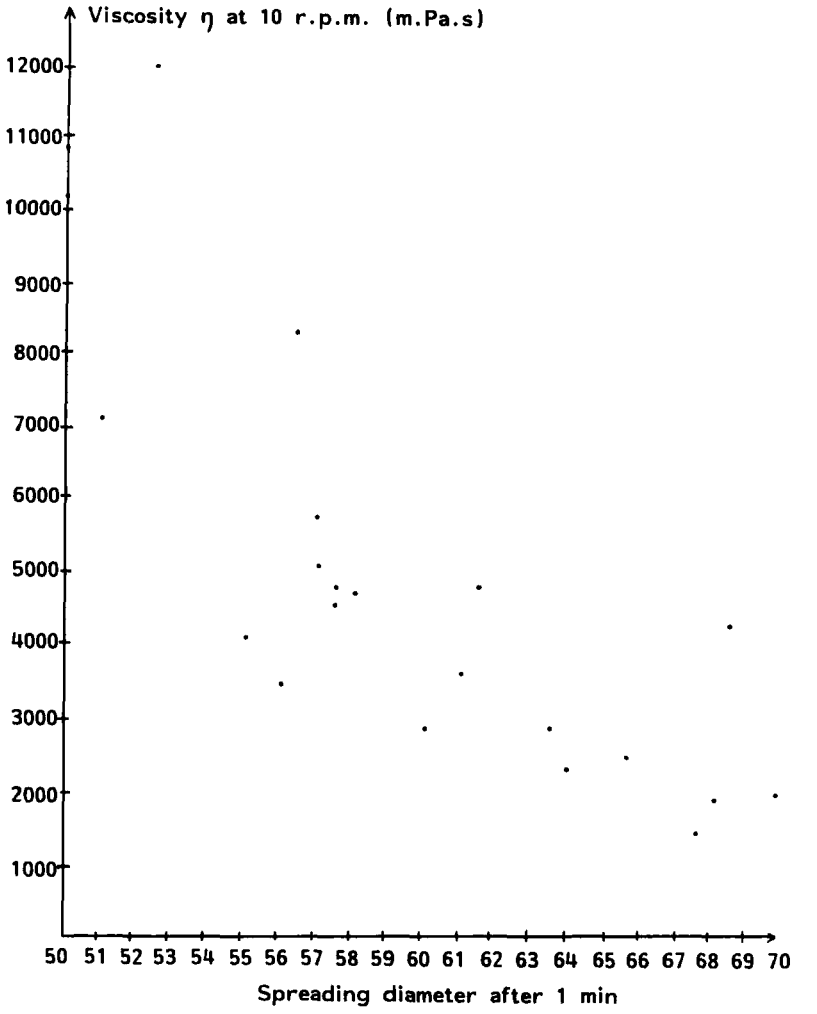

FIGURE 4

Gels based on carraghenans.

Relationship between viscosity and spreading diameter

evaluated by measuring spreading diameter and rheological behaviour. Spreading diameter and viscosity were linearly related in the gels based on cellulose gelling agents, but not in those based on carraghenans, which were pseudoplastic and thixotropic.

Stability tests are presently being carried out on the formulations that were found satisfactory here. They concern the stability of the procyanidins and the physical stability of the gels, the latter is assessed by monitoring the spreading diameter of the cellulose-based gels and the viscosity of the carraghenan-based gels. The results of these tests will be published in due course.

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