DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(15), 2083-2092 (1991)

A DOSAGE FORM FOR PROCYANIDINS GELS BASED ON CELLULOSE DERIVATIVES

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ABSTRACT

The formulation of procyanidin gels based on cellulose derivatives is described. Type and optimal concentration of gelling agents were determined to obtain stable, limpid gels of satisfactory viscosity and pH compatible with anti-ulcer therapy.

INTRODUCTION

In previous work we prepared procyanidins by fermentation of an extract of rhizomes of *Fragaria vesca* (1-3). They consisted mainly of dimers along with a small proportion of monomers (4). Procyanidins have been shown to possess angioprotective properties and an appreciable anti-ulcer activity in Rat (5-6). We studied their use as a raw material for preparing active complexes (7-8). Direct compression tablets (9) and effervescent dosage forms, particularly suited to anti-ulcer therapy (10-13) were developed. We report here the results of work on the preparation of procyanidin gels. This form is often used for administration of antiacids (14)

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because of its high coating power. The gelling agents tested were all cellulose derivatives.

MATERIALS AND METHODS

Raw Materials

The following cellulose derivatives were tested as gelling agents. Methylcellulose : Metolose SM 400® (FMC Corp. Seppic), Viscontran MC 400®, Viscontran MC 3000 P® (Henkel) ; Carboxymethylcellulose : sodium CMC® (Prolabo), Blanose 7 HFD® , Blanose 7 HOF® (Aqualon) ; Hydroxyethylcellulose : Natrosol 250 G® (Aqualon), Tylose H 10000 P® (Hœchst) ; Hydroxypropylcellulose : Klucel GFNF® (Aqualon) ; Hydroxypropylmethylcellulose : Viscontran MHPC 6000® (Henkel), Metolose 90 SH 15000®, Metolose 65 SH 4000® (FMC Corp. Seppic).

The procyanidins incorporated into the gels were prepared by us (3).

Methods

Preparation of Gels

The gelling agent was dispersed in water at 35°C with an IKA RW20 helical stirrer. The stirring rate was set at 500 r.p.m. for formulations 1 to 32, 250 r.p.m. for formulations 33 to 36 and 150 r.p.m. for formulations 37 to 48. The dispersion of 600 g of gel took 20 minutes.

Determination of Spreadability

One gram of gel 48 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.

Evaluation of Opalescence

The opalescence of the gels was studied using the method described in the French Pharmacopœia (15), and spectrophotometric measurement of the transmission at 610 nm of reference solutions and tested gels.

Appraisal of Foaming Power of Gelling Agent on Dispersal

Under the conditions described above, 100 g of gel was prepared in a 250 ml beaker (Ø = 73 mm, h = 90 mm). The height of the foam remaining 30 min after the end of dispersion was measured.

Rheological Study

A rheological study of the procyanidin gels was carried out at 21°C using a Brookfield RVTD V2® instrument fitted with an SC4-28/13R Small Adapter, mobile 5.

Measurement of the Stability of the Procyanidins

Five grams of gel were placed in a 100 ml graduated flask containing 50 ml of water. The flask was left for five minutes in an ultrasonic bath and then topped up to the mark with water. A 20 µl sample of this solution was analysed by HPLC under the following conditions : column : LiChrosorb RP 18 5 µm (60 x 4.6 mm) (Interchim); gradient : two-solvent system with A = HCOOH-H_2O (1 : 19), B = CH_3OH, 0-1.5 min 7 % B (isocratic), 1.5 -10.5 min 7 - 51 % B in A (linear gradient), 10.5 - 13.5 min 51 - 80 % B in A (linear gradient), 13.5 - 15 min 80 % B (isocratic); flow-rate 2.2 ml/min ; temperature 21°C; column pressure 150 kg/cm^2; detection by UV at 280 nm.

RESULTS AND DISCUSSION

Preparation of Placebo Gels

Forty-eight gels were prepared, all containing 0.15 % Nipagine® and differing in the type and concentration of the gelling agent. Five types of cellulose derivatives were tested, methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses, hydroxypropylcelluloses, hydroxypropylmethylcelluloses. These agents are widely used in dosage forms as they have high water solubility and at a concentration of 1 % (w/v) give limpid hydrogels with pH values close to neutral (16). However, hydroxypropylcelluloses and hydroxypropylmethylcelluloses present the drawback that they strongly lower the surface tension of water and so generate foam during dispersion (17).

TABLE 1

Methylcellulose-based Gels. pH and Spreadability

Formulation n°	Gelling Agent	Concentration % (w/w)	pH	Spreading Diameter after 1 min (mm)
1	Metolose SM 400	2	7.75	98
2	Metolose SM 400	3	7.75	77
3	Metolose SM 400	4	7.80	69
4	Metolose SM 400	5	7.80	57
5	Viscontran MC 400	2	7.70	97
6	Viscontran MC 400	3	7.80	78
7	Viscontran MC 400	4	7.80	66
8	Viscontran MC 400	5	7.85	54
9	Viscontran MC 3000 P	1	7.70	82
10	Viscontran MC 3000 P	2	7.70	71
11	Viscontran MC 3000 P	3	7.75	58
12	Viscontran MC 3000 P	4	7.75	49

TABLE 2

Carboxymethylcellulose-based Gels. pH and Spreadability

Formulation n°	Gelling Agent	Concentration % (w/w)	pH	Spreading Diameter after 1 min (mm)
13	Sodium CMC	2	8.00	92
14	Sodium CMC	3	8.10	65
15	Sodium CMC	4	8.20	59
16	Sodium CMC	5	8.30	44
17	Blanose 7 HFD	1	8.20	75
18	Blanose 7 HFD	1.5	8.30	60
19	Blanose 7 HFD	2	8.35	50
20	Blanose 7 HFD	2.5	8.40	43
21	Blanose 7 HOF	1	8.15	77
22	Blanose 7 HOF	1.5	8.25	62
23	Blanose 7 HOF	2	8.30	54
24	Blanose 7 HOF	2.5	8.30	45

The different formulations were compared according to four main criteria : pH, spreadability, limpidity and foaming during dispersion.

pH and Spreadability

As shown in Tables 1 to 5 all the gels prepared had satisfactory pH values ranging between 7.30 for formulation 44 and 8.40 for formulation 20.

TABLE 3

Hydroxyethylcellulose-based Gels. pH and Spreadability

Formulation n°	Gelling Agent	Concentration % (w/w)	pH	Spreading Diameter after 1 min (mm)
25	Natrosol 250 G	3	7.80	93
26	Natrosol 250 G	4	7.75	78
27	Natrosol 250 G	5	7.70	59
28	Natrosol 250 G	6	7.70	50
29	Tylose H 10000 P	1.5	7.60	71
30	Tylose H 10000 P	2	7.60	59
31	Tylose H 10000 P	2.5	7.55	47
32	Tylose H 10000 P	3	7.50	45

TABLE 4

Hydroxypropylcellulose-based Gels. pH and Spreadability

Formulation n°	Gelling Agent	Concentration % (w/w)	pH	Spreading Diameter after 1 min (mm)
33	Klucel GFNF	3	7.65	83
34	Klucel GFNF	4	7.65	60
35	Klucel GFNF	5	7.60	58
36	Klucel GFNF	6	7.60	56

TABLE 5

Hydroxypropylmethylcellulose-based Gels. pH and Spreadability

Formulation n°	Gelling Agent	Concentration % (w/w)	pH	Spreading Diameter after 1 min (mm)
37	Viscontran MHPC 6000	1	7.70	102
38	Viscontran MHPC 6000	2	7.75	89
39	Viscontran MHPC 6000	3	7.70	63
40	Viscontran MHPC 6000	4	7.70	54
41	Metolose 90 SH 15000	1	7.40	88
42	Metolose 90 SH 15000	2	7.35	77
43	Metolose 90 SH 15000	3	7.35	60
44	Metolose 90 SH 15000	4	7.30	52
45	Metolose 65 SH 4000	1	7.80	104
46	Metolose 65 SH 4000	2	7.80	91
47	Metolose 65 SH 4000	3	7.75	72
48	Metolose 65 SH 4000	4	7.75	58

TABLE 6

Assessment of Limpidity of Gels

Formulation n°	Gelling Agent	Concentration % (w/w)	T % (610 nm)
3	Metolose SM 400	4	18
4	Metolose SM 400	5	14
7	Viscontran MC 400	4	12
8	Viscontran MC 400	5	10
11	Viscontran MC 3000 P	3	26
14	Sodium CMC	3	96
15	Sodium CMC	4	94
18	Blanose 7 HFD	1.5	98
22	Blanose 7 HOF	1.5	98
23	Blanose 7 HOF	2	98
27	Natrosol 250 G	5	97
30	Tylose H 10000 P	2	93
34	Klucel GFNF	4	92
35	Klucel GFNF	5	90
36	Klucel GFNF	6	87
40	Viscontran MHPC 6000	3	64
43	Metolose 90 SH 15000	3	73
44	Metolose 90 SH 15000	4	70
48	Metolose 65 SH 4000	4	71

Their spreading diameter after one minute is an indication of their viscosity (18).

Under the present experimental conditions, the following classification was adopted semi-stiff gels $\emptyset \leq 70$ mm, semi-fluid gels $50 < \emptyset < 70$ mm and fluid gels $\emptyset > 70$ mm. As most of the anti-acid gels currently on the market (14) are semi-fluid, only 19 formulations were retained for further testing, i.e. formulations 3, 4, 7, 8, 11, 14, 15, 18, 22, 23, 27, 30, 34, 35, 36, 40, 43, 44 and 48.

Limpidity

The limpidity of the gels was assessed by the method described in the French Pharmacopoeia (15) and by transmission spectrophotometry at 610 nm (Table 6). Under these conditions, four types of gel can be distinguished ; limpid gels $T\% \geq 80$, slightly opalescent gels $80 < T\% < 42$, opalescent gels $42 \leq T\% < 22$ and very opales-

TABLE 7

Assessment of Foaming Power of Gelling Agent on Dispersion

Formulation n°	Gelling Agent	Concentration % (w/w)	H (mm)
14	Sodium CMC	3	0
15	Sodium CMC	4	0
18	Blanose 7 HFD	1.5	0
22	Blanose 7 HOF	1.5	0
23	Blanose 7 HOF	2	0
27	Natrosol 250 G	5	4
30	Tylose H 10000 P	2	1
34	Klucel GFNF	4	7.5
35	Klucel GFNF	5	9
36	Klucel GFNF	6	9.5

TABLE 8

Characteristics of Procyanidin Gels

Formulation n°		49	50	51	52	53	54	55
Raw Materials %	Procyanidins	1	1	1	1	1	1	1
	Sodium CMC	3	4					
	Blanose 7 HFD			1.5				
	Blanose 7 HOF				1.5	2		
	Natrosol 250 G						5	
	Tylose H 10000 P							2
	Nipagine	0.15	0.15	0.15	0.15	0.15	0.15	0.15
pH		7.90	7.95	8.0	8.0	8.05	7.60	7.50
Spreading Diameter (mm)		65	58	60	61	54	59	60
Viscosity at 5 r.p.m. (m.Pa.s.)		5100	23000	19700	18100	40400	22500	20200

cent gels T % $\leqslant$ 22. Only those formulations yielding limpid gels were retained for further tests, i.e. formulations 14, 15, 18, 22, 23, 27, 30, 34, 35 and 36.

Foaming Power of Gelling Agent on Dispersion

Tendency to foam was assessed by measuring the height of foam H remaining 30 minutes after dispersion. Only those formulations

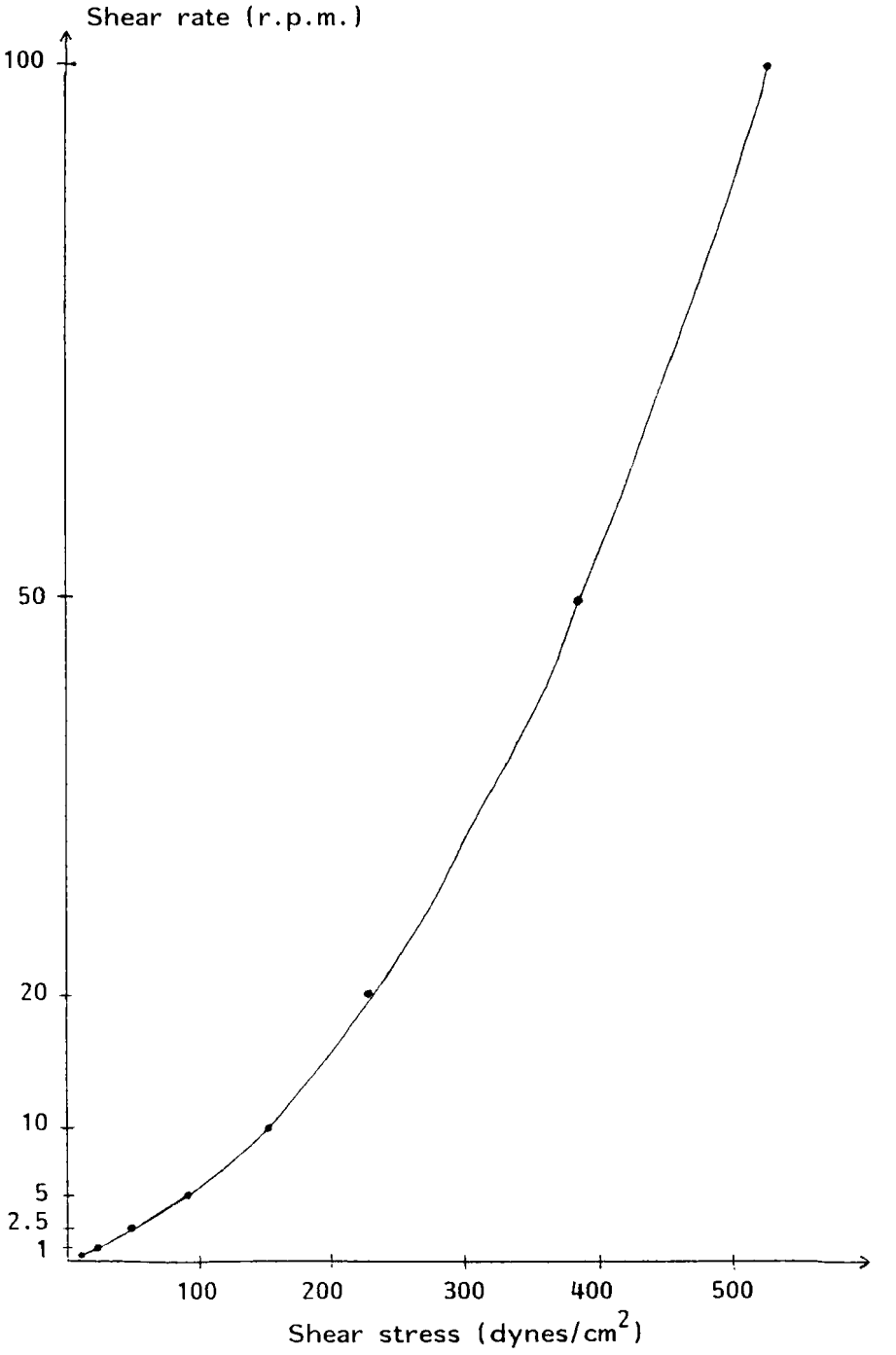

FIGURE 1

Rheogram of Procyanidin Gel (Formulation n° 51)

from Brookfield RVTDV2® Viscosimeter

for which H ⩽ 5 mm were retained. This test (Table 7) confirmed the drawback that the hydroxypropylmethylcelluloses (Klucel GFNF®) have of lowering the surface tension of the water.

The carboxymethylcelluloses (sodium CMC® and Blanose®) caused no foaming, however, and the small amount of foam generated by the hydroxyethylcelluloses (Natrosol 250 G® and Tylose H 10000 P ®) vanished completely after one hour.Formulations 14, 15, 18, 22, 23 27 and 30 were thus finally retained.

Preparation and Analysis of Procyanidin Gels

Characteristics of the Gels

We prepared gels containing 1 % procyanidins from each of the seven formulations finally retained. All had satisfactory pH and spreading diameters close to those measured for the placebo gels (Table 8).

The rheological study of these semi-fluid gels showed them to be pseudoplastic and non-thixotropic, as exemplified by the rheogram of formulation 51 (Figure 1).

The viscosity of the different preparations ranged between 5100 m.Pa.s. (formulation n° 49) and 40400 m.Pa.s. (formulation n° 53).

Stability of Procyanidins

The gels were stored under the following conditions : exposed to light at 22°C, in the dark at 22°C, in the dark at 37°C and in the dark at 4°C. The stability of the procyanidins in the gels was evaluated by HPLC (9). After one year, the HPLC spectrum of the procyanidins remained unchanged for all four conditions of storage.

CONCLUSION

We have prepared a series of stable, limpid procyanidin gels of satisfactory viscosity and pH compatible with anti-ulcer therapy.

Gels based on carraghenanes and alginates are being developed and results will be published shortly.

ACKNOWLEDGEMENTS

The authors thank Paul Legret for technical assistance.

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