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COMPARISON OF THE PHYSICAL STABILITY OF ASTRINGENT HYDROGELS BASED ON CELLULOSE DERIVATIVES

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ABSTRACT

Formulation and physical stability of hamamelis gels, using as gelling agents cellulose derivatives, were studied. Gelled vehicles were selected according two criteria : spreading diameter and limpidity.

The tests of physical stability applied to the hamamelis gels showed four of them to have the required stability : one based on methylcellulose Benecel M 142C®, one based on hydroxyethylcellulose, Natrosol 250G® and two based on hydroxypropylcellulose, Klucel M® and Klucel H®.

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INTRODUCTION

Extracts of *Hamamelis virginiana* (Hamamelidaceae) contain a specific hydrolysable tannin, hamamelitannin (1) and condensed tanins or proanthocyanidin polymers (2, 3) several of which we have identified (4). We recently reported a qualitative and quantitative analysis of the polyphenols from a fluid extract of hamamelis codex leaves (5), subsequently, we developed methods of identification and assay suitable for routine use (6). Being in possession of a perfectly codified extract (7), mostly of known composition , together with reliable assay methods, we could proceed to the development of dosage forms of this extract. We focused on pharmaceutical applications : hamamelis extract, which is particularly rich in proanthocyanidins,exhibits angioprotector properties which make it useful for the treatment of circulatory disorders. Accordingly we recently undertook a study of the formulation of tablets by direct compression (8).
Hydrogel is a dosage form well-suited for local treatment of circularoty disorders. We therefore report here the formulation and the physical stability of hamamelis gels using as gelling agents cellulose derivatives which we had studied previously (9, 10).

MATERIAL AND METHODS

Raw Materials

Fluid hamamelis extract was laboratory prepared under the conditions prescribed by the French Pharmacopoeia (7).

The following cellulose derivatives were tested as gelling agents : methylcelluloses : Benecel MC 4000 PS® and Benecel Me 142C (Aqualon) ; carboxymethylcelluloses : Sodium CMC (Prolabo), Blanose 7HFD and Blanose 7HOF (Aqualon) ; hydroxyethylcelluloses : Natrosol 250G

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(Aqualon) and Tylose H10000P (Hoechst) ; hydroxypropylcelluloses :Klucel M and Klucel H (Aqualon) ; methylhydroxypropylcelluloses : Benecel MP 324C (Aqualon).

Methods

Preparation of gels

The gelling agent was dispersed in water using a Stephan UMC 5 electronic apparatus at 35°C for formulations 3 to 7 and 13 to 17, at 20°C for formulations 8, 9 and 19, and at 10°C for formulations 1, 2, 10, 11, 12 and 20. The stirring rate was set at 1200 r.p.m. The gelified vehicle was maintained under vacuum and with stirring for 15 minutes before incorporating the fluid hamamelis extract with a lower stirring rate (900 r.p.m.) (formulations 11 to 20).

Determination of spreading capacity

48 h after preparation, the spreading diameter of 1 g of the gel between two glass plates (20 x 20 cm) was measured after 1 min (mass of the upper plate 125 g).

Evaluation of opalescence of placebo gels

The opalescence of the gels was studied using the method described in the European Pharmacopoeia (11), completed with spectrophotometric measurement of the transmission at 610 nm of reference solutions and the tested gels.

Rheological study of hamamelis gels

This study was performed at 21°C, using a Brookfield RVTD V2 viscometer fitted with a Small Adapter SC4-28/13R system.

Test of physical stability of gels

Four conditions of storage were studied : (i) in the dark at 30°C in a Memmert oven, (ii) in the light at room temperature (21°C ± 2°C), (iii) in the dark at room temperature (21°C ± 2°C) and (iv) in the dark at 4°C in a cold room. The stability of the gels was assessed by rheological measurements at regular time intervals.

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RESULTS AND DISCUSSION

Formulation

We formulated hamamelis gels using as gelling agents cellulose derivatives. Five types of derivatives were tested, methylcelluoses (MC), carboxymethylcelluloses (CMC),hydroxyethylcelluloses(HEC), hydroxypropylcelluloses (HPC) and hydroxypropylmethylcelluloses (HPMC). Theses agents are widely used in dosage forms as they have a high water solubility. However, HPC and HPMC present the drawback that they strongly lower the surface tension of water and so generate foam during dispersion. For each type of cellulose derivatives, several commercial products were tested ; these differed in the degree of substitution and polymerisation.

In recent work, we developed ten formulations for gelled vehicles with a limpidity and a semi-fluid consistency suitable for skin application (12). All these formulations contained 0.15 % Nipagine and were selected according to the following two criteria (table 1) :

(i) spreading diameter after one minute, which is a measure of consistency ; under the experimental conditions developed (9, 10), a semi-fluid gel as spreading diameter of between 50 and 70 mm. (ii) percent transmission at 610 nm which evaluates the limpidity ; under experimental conditions, a limpid gel has T% > 80 (9, 10).

The pH of these ten placebo gels ranged from 7.6 and 9.0. These seemingly high values were considered acceptable however, since preliminary trials had shown that the addition of fluid hamamelis extract appreciably lowered the pH of the gelled vehicle. In addition, for the HPC and MHPC (formulations 8, 9 and 10) it was possible to avoid foaming by dispersing the gelling agent in a vacuum using a UMC 5 electronic apparatus.

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Table 1

Characteristics of Placebo Gels based on Cellulose Derivatives

Cellulose derivative	Gelling agent	Concentration % (w/w)	pH	Ø after 1 min (mm)	T % at 610 nm	Formulation n°
MC	Benecel MC4000PS	2.5	8.7	60	83	1
	Benecel Me 142C	4.5	9.0	54.5	79	2
CMC	Sodium CMC	4.0	8.2	59	96	3
	Blanose 7HFD	2.0	8.3	50	97	4
	Blanose 7HOF	2.0	8.3	54	98	5
HEC	Natrosol 250G	6.0	7.7	50	97	6
	Tylose H10000P	2.0	7.6	59	93	7
HPC	Klucel M	2.0	8.4	58.5	97	8
	Klucel H	1.5	8.3	57	94	9
MHPC	Benecel MP324C	1.5	9.0	60.5	88	10

The characteristics of the corresponding hamamelis gels are shown in table 2. The neutralising effect of the fluid hamamelis extract on the pH of the final gel is apparent. In most cases, addition of 0.5% (w/w) of this extract also caused an increase in spreading diameter, though this remained within the limits previously set.

The rheological study of these gels showed a viscosity ranging from 3 120 m.Pa.s. for formulation 11 to 5940 m.Pa.s. for formulation 16, and indicated pseudoplactic and non-thixotropic behaviour.

In previous work on the formulation of procyanidin gels based on cellulose derivatives, we demonstrated a linear relationship between spreading diameter and viscosity (10). Figure 1 shows that this relationship also exists for the hamamelis gels studied ; linearity is observed for semi-fluid gels with spreading diameters in the range 54 to 63 mm.

Test of physical stability of gels

Stability was studied under four conditions of storage : in the dark at 30°C, in the light at 21°C ± 2°C, in the dark at 21°C ± 2°C and in the dark at 4°C.

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Table 2

Characteristics of Hamamelis Gels based on Cellulose Derivatives

Formulation n°*	Gelled vehicle : Cellulose derivative	pH	Ø (mm) after 1 min	η (m.Pa.s.) at 10 r.p.m.
11	(MC)Benecel MC4000PS 2.5% (w/w)	7.6	61	3120
12	(MC)Benecel Me 142 C 4.5% (w/w)	7.6	59	4450
13	(CMC) Sodium CMC 4% (w/w)	7.5	59.5	4060
14	(CMC) Blanose 7HFD 2% (w/w)	7.6	58	5000
15	(CMC) Blanose 7HOF 2% (w/w)	7.7	60	3780
16	(HEC)Natrosol 250G 6% (w/w)	6.9	57	5940
17	(HEC) Tylose H10000P 2% (w/w)	6.8	60.5	3460
18	(HPC) Klucel M 2% (w/w)	7.2	58.5	4940
19	(HPC) Klucel H 1.5% (w/w)	7.2	57.5	5340
20	(HEMC)Benecel MP324C 1.5% (w/w)	7.7	60.5	3560

*Each gel contains 0.5% (w/w) of hamamelis extract

The stability of the different hamamelis gels was evaluated by the following criterion : a gel is considered stable when no change in consistency is perceptible to the touch. The gels studied had spreading diameters in the range 57 to 61 mm : we observed that a change in consistency (fluidification) became perceptible when the spreading diameter reached 65 mm. We set the maximum spreading diameter not at 65 mm but at 63 mm, the upper limit of the spreading diameter versus viscosity linearity (figure 1). From the equation for the straight line $\eta = F(\emptyset)$, a diameter of 63 mm corresponds to a viscosity of 1750 m.Pa.s. at 10 r.p.m.

For each storage condition, each gel was subjected to rheological measurements at regular time intervals, the limit of acceptable stability being taken as 1750 m.Pa.s.

Stability in the dark at 30°C

As shown in table 3, stability depends on the type of cellulose derivative.

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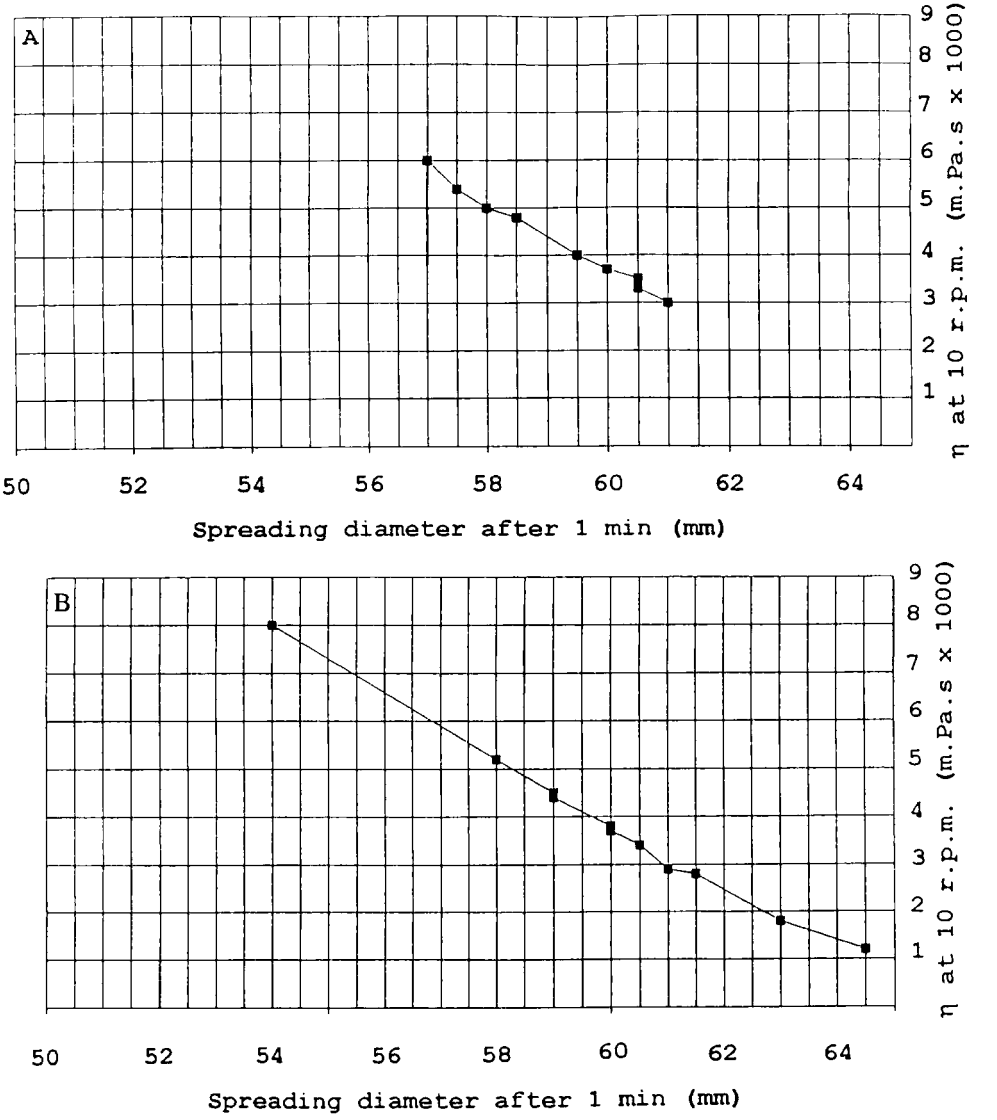

Figure 1

Cellulose-based gels. Spreading diameter versus viscosity : **A** Hamamelis gels (table 2) ; **B** Procyanidin gels (10). Equations for the two straight lines : $y = 10650 - 684.6\ x$

x (mm) = Ø - 50 ; y (m.Pa.s.) = η at 10 r.p.m.

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Table 3

Stability of Hamamelis Gels in the Dark at 30°C

Formulation n°*	Cellulose derivative	Limit of stability (days)	η (m.Pa.s.) at 10 r.p.m. after 800 days
11	(MC)Benecel MC4000PS	60	-
12	(MC)Benecel Me142C	120	-
13	(CMC) Sodium CMC	150	-
14	(CMC) Blanose 7HFD	40	-
15	(CMC) Blanose 7HOF	40	-
16	(HEC)Natrosol 250G	250	-
17	(HEC)Tylose H10000P	25	-
18	(HPC) Klucel M	280	-
19	(HPC) Klucel H	-	2950
20	(HPMC)Benecel MP324P	60	-

Storage in the dark at 30°C rapidly affected the viscosity of the gels based on **methylcelluloses carboxymethylcelluloses** and **methylhydroxypropylcellulose.**

For the formulations based on **hydroxyethylcelluloses,** the Natrosol 250 G® gel was stable for more than 250 days at 30°C, while the Tylose H 10000 P® gels lasted less than 25 days.

The best results were obtained with the **hydroxypropylcelluloses.** The stability limit of formulation 18 based on Klucel M® exceeded 280 days. The viscosity of formulation 19 based on Klucel H® was still satisfactory (about 3000 m.Pa.s.) after more than 800 days storage in the dark at 30°C.

Stability in the light at ambient temperature

As shown in table 4, stability of the **methylcelluloses**-based gels depends on the type of substitution of the derivative tested ; the stability of formulation 11 based on simple methylcellulose, Benecel MC 4000 PS®, hardly exceeded 90 days, whereas the gel based on a methylethylcellulose Benecel Me 142 C® remained perfectly stable after more than 800 days storage in the light at ambient temperature.

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Table 4

Stability of Hamamelis Gels in the Light at Room Temperature

Formulation n°*	Cellulose derivative	Limit of stability	η (m.Pa.s.) at 10 r.p.m. after 800 days
11	(MC)Benecel MC4000PS	90	-
12	(MC)Benecel Me 142 C	-	4400
13	(CMC) Sodium CMC	200	-
14	(CMC) Blanose 7HFD	75	-
15	(CMC) Blanose 7HOF	75	-
16	(HEC)Natrosol 250G	-	4000
17	(HEC) Tylose H10000P	100	-
18	(HPC) Klucel M	-	2900
19	(HPC) Klucel H	-	3000
20	(HPMC)Benecel MP324P	75	-

Gels based on **carboxymethylcelluloses** and **methylhydroxypropylcellulose** present a poor stability.

Of the formulations based on **hydroxyethylcelluloses**, stability depends on the degree of polymerization : the Natrosol 250 G® gel was the most stable, with a viscosity close to 4000 m.Pa.s. after 800 days storage in the light at ambient temperature. In contrast, formulation 17 based on a less polymerized derivative, Tylose H 10000 P®, remained stable for only 100 days.

Here again, the best results were obtained with the **hydroxypropylcelluloses**. The gels based on Klucel M® and Klucel H® (formulations 18 and 19) still had viscosities of about 3000 m.Pa.s. after 800 days in the light and at ambient temperature.

Stability in the dark at ambient temperature

The results of these stability tests were comparable to those obtained in the light at ambient temperature (table 5).

For gels based on **methylcelluloses** (table 6), the stability of formulation 11 based on Benecel MC 4000 PS® reached barely 180 days while the gel based on Benecel Me 142 C® (formulation 12) remained perfectly stable after more than 800 days storage in the dark at 4°C.

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Table 5

Stability of Hamamelis Gels in the Light at Room Temperature

Formulation n°*	Cellulose derivative	Limit of stability	η (m.Pa.s.) at 10 r.p.m. after 800 days
11	(MC)Benecel MC4000PS	190	-
12	(MC)Benecel Me 142 C	-	4650
13	(CMC) Sodium CMC	200	-
14	(CMC) Blanose 7HFD	80	-
15	(CMC) Blanose 7HOF	80	-
16	(HEC)Natrosol 250G	-	4000
17	(HEC) Tylose H10000P	100	-
18	(HPC) Klucel M	-	2900
19	(HPC) Klucel H	-	3000
20	(HPMC)Benecel MP324P	80	-

Table 6

Stability of Hamamelis Gels in the Dark at 6°C

Formulation n°*	Cellulose derivative	Limit of stability	η (m.Pa.s.) at 10 r.p.m. after 800 days
11	(MC)Benecel MC4000PS	220	-
12	(MC)Benecel Me 142 C	-	3750
13	(CMC) Sodium CMC	-	3950
14	(CMC) Blanose 7HFD	260	-
15	(CMC) Blanose 7HOF	240	-
16	(HEC)Natrosol 250G	-	5750
17	(HEC) Tylose H10000P	-	2400
18	(HPC) Klucel M	-	3450
19	(HPC) Klucel H	-	3800
20	(HPMC)Benecel MP324P	300	-

Stability in the dark at 4°C

For the formulation based on **carboxymethylcelluloses,** this test confirmed the marked superiority of the highly polymerized Sodium CMC ; after 800 days storage in the dark at 4°C, formulations 13 still had a satisfactory viscosity (close to 4000 m.Pa.s.). The stability of formulations 14 and 15, prepared respectively with Blanose 7HFD® and Blanose 7HOF® lasted no more than 200 days.

The stabilities of the formulations based on **hydroxyethylcelluloses** were highly satisfactory, particularly for the Natrosol 250G® gel whose viscosity was practically unchanged after 800 days storage in the dark at 4°C.

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The gels based on **hydroxypropylcelluloses** also displayed a satisfactory stability of about 800 days.
This was not the case for formulation 20 based on **methylhydroxypropylcellulose**, which was stable for barely 250 days in the same conditions.

CONCLUSION

This work exemplifies the difficulty of choosing a suitable cellulose derivative for the formulation of a hydrogel.
The properties of the various gels tested vary according to the type of cellulose derivative ; in addition, for a given type of derivative ther are often several commercial products differing in their degrees of substitution and polymerisation, which influence their gelling power and the stability of the gels.

The tests of physical stability applied to ten hamamelis gel formulations showed four of them to have the required stability : one based on a methylethylcellulose, Benecel Me 142C® (formulation 12), one based on a hydroxyethylcellulose, Natrosol 250G® (formulation 16) and two based on hydroxypropylcellulose Klucel M® and Klucel H® (formulations 18 and 19).

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