Drug Development and Industrial Pharmacy, 24(1), 27–35 (1998)

RESEARCH PAPER

Comparative Texturometric Analysis of Hydrogels Based on Cellulose Derivatives, Carraghenates, and Alginates: Evaluation of Adhesiveness

B. Vennat, F. Lardy, A. Arvouet-Grand, and A. Pourrat*

Service de Pharmacie Galénique et Pharmacotechnie UFR Pharmacie 28, place H. Dunant, BP 38, 63001 Clermont-Ferrand cedex, France

ABSTRACT

This paper reports a texturometric study of hydrogels based on cellulose derivatives, carraghenates (with or without Na^+ or K^+), and alginates (associated or not with Ca^{++}). The stiffness, elasticity, and cohesiveness are evaluated and the influence of the nature and the concentration of gelling agent on the adhesiveness, an indicator of bioadhesion, is discussed.

The highest adhesiveness values are found among the semi-stiff gels, particularly with those based on either sodium or potassium alginate, or cellulose derivatives. The least satisfactory results are obtained with the formulations associating carraghenates and Na^+ or K^+.

INTRODUCTION

In the course of work on practical applications of naturally occurring substances, we have been developing the use of procyanidin extracts in pharmaceutical dosage forms.

Two such applications are currently being studied: topical treatment of circulation disorders in the lower limbs and anti-ulcer treatment. We have focused on hydrogel delivery forms, which are particularly well suited to these two therapies.

We studied three types of gelling agent: cellulose derivatives, carraghenates, and alginates. Formulation was based on several physical and chemical criteria: pH, limpidity, spreadability, and rheological behavior. Stability in real time and under accelerated aging was also measured.

For the cellulose derivatives, we studied the influence of the nature of the substituent, the degree of substitution, and the degree of polymerization on the physical and chemical characteristics and stability of the hydrogels (1,2). These studies showed that hydroxyethyl-

*To whom correspondence should be addressed.

celluloses and hydroxypropylcelluloses with high degrees of substitution and polymerization were best suited. For carraghenates, it was found that the most stable gels were obtained with the hydrocolloids richest in κ and ι gelling fractions, associated or not with a reticulating agent, sodium, or potassium citrate (3,4). Finally, we showed that the physical and chemical properties and the stability of the gels based on alginates depended on the type of alkaline alginate tested and its degree of polymerization. Their performance was improved by the presence of a reticulating agent, calcium gluconate (4,5).

These results enabled us to select the best-performing gel vehicles. We report here a texturometric study designed to evaluate their stiffness, elasticity, cohesiveness, and adhesiveness. We paid special attention to this last property, considered to be an indicator of bioadhesion (6,7). Bioadhesion of an antacid or topical gel affords more prolonged local concentration of the active ingredients, which can improve therapeutic effectiveness.

MATERIALS AND METHODS

Materials

The following gelling agents were tested. Cellulose derivatives (Aqualon, France) hydroxyethylcellulose Natrosol 250 G®; and were hydroxypropylcelluloses Klucel 99 MF-EP® and Klucel 98 HF-EP®. Carraghenates (Systems Bio-Industries, France) were Satiagum UTC 10®; and Satiagel CT 52®; associated or not with a reticulating agent, sodium or potassium citrate (Prolabo, France). Alginates were sodium alginate Satialgine S1600® (Systems Bio-Industries) and potassium alginate Kelmar® (Kelco, France), associated or not with a reticulating agent, calcium gluconate; and sodium calcium alginate Kelset® (Kelco).

Methods

Preparation of Hydrogels

The gelling agents were dispersed in water containing 0.15% (w/w) Nipagine® and when appropriate the reticulating agent, using an IKA RW20 DZM stirrer. The dispersion was carried out at 20°C for the cellulose derivatives and alginates, and at 35°C for the carraghenates. The stirring rate was 500 rpm.

Determination of Spreadability

The spreadability of the hydrogels was estimated at 21 ± 0.5°C 48 hr after preparation as follows: The spreading diameter (ϕ) of 1 ± 0.01 g of gel placed between two horizontal glass plates (20 × 20 cm) was measured after 1 min (mass of the upper plate: 125 ± 1 g) using a previously validated protocol (8). The following classification was applied: fluid gels $\phi > 70$ mm, semi-fluid gels 50 mm $\leq \phi \leq$ 70 mm, semi-stiff gels $\phi < 50$ mm.

Rheological Study

A rheological study was carried out at 21 ± 0.5°C using a Brookfield RVTD V2 viscometer fitted with an SC4-28/13R small sample adapter.

Texturometric Analysis

Texturometric analysis was carried out at 21°C using an Etia T04 texturometer fitted with a 50N sensor. Each of the gels was packed in a 500-g jar and analyzed in its original container, without stirring or shaking.

Compression–Relaxation Study

A compression–relaxation study was performed with a cylindrical plate probe of diameter 50 mm, in the following conditions: speed of travel 0.6 mm/sec, compression depth 5 mm, relaxation time 15 sec, test duration 25 sec.

Two-Cycle Test

A two-cycle test was carried out using a cylindrical holed plate probe (plate diameter 70 mm, diameter of holes 7.4 mm) in the following conditions: speed of travel 0.6 mm/sec, compression depth 4 mm, compression duration 6.7 sec, height of withdrawal between the two cycles 60 mm for the 8% Natrosol 250G gel and 40 mm for the other gels.

RESULTS AND DISCUSSION

Characteristics of Hydrogels Tested

In each class of gelling agent and for each of the commercial products tested, we prepared two gelled vehicles with different consistencies: a semi-fluid gel of spreading diameter in the range 50–70 mm and a semi-stiff gel of spreading diameter less than 50 mm.

The characteristics of the different formulations are given in Tables 1, 2 and 3. There was some correlation between viscosity and spreading diameter for the hydrogels based on cellulose derivatives, but not for those based on carraghenates or alginates (5,9).

Table 1

Characteristics of Hydrogels Based on Cellulose Derivatives

Formulation No.	1	2	3	4	5	6
Constituents (% w/w)						
HEC:Natrosol 250 G	5	8				
HPC:Klucel 99 MF-EP			2	3		
HPC:Klucel 98 HF-EP					1.5	2.5
Viscosity at 2.5 rpm (10^3 mPa·sec)	6.24	46.9	6.0	36.1	6.4	37.0
Spreading diameter after 1 min (mm)	61	47	61	49	60	49

Table 2

Characteristics of Hydrogels Based on Carraghenates

Formulation No.	7	8	9	10	11	12	13	14
Constituents (% w/w)								
Satiagum UTC10	24	3						
Satiagel CT 52			2	3	1.2	2.828	1.5	2.5
Sodium citrate					0.88	2.05		
Potassium citrate							1.02	1.7
Viscosity at 2.5 rpm (10^3 mPa·sec)	5.12	48.4	6.64	48.4	14.9	47.2	5.36	38.6
Spreading diameter after 1 min (mm)	62	48	61	44	62	44	58	48

Table 3

Characteristics of Hydrogels Based on Alginates

Formulation No.	15	16	17	18	19	20	21	22	23	24
Constituents (% w/w)										
Satialgine S1600	2	3.5	1.5	2.5						
Kelmar					2.5	4	2	3		
Kelset									12	17
Calcium gluconate			0.18	0.3			0.15	0.225		
Viscosity at 2.5 rpm (10^3 mPa·sec)	3.04	23.3	4.32	58.0	4.32	31.1	15.1	68.0	25.0	70.0
Spreading diameter after 1 min (mm)	62	48	57	44	60	45	53	40	53	45

Texturometric Analysis

This analysis was in two parts: a compression–relaxation study and two-cycle study.

In the first study, the probe distorts the sample for a set time, and the response in Newtons (N) indicates its stiffness.

The two-cycle study quantifies adhesiveness, elasticity, and cohesiveness (Fig. 1). The adhesiveness is the negative work measured when the probe is withdrawn from the sample. The ratio of the compression durations of the second and first cycles indicates the elasticity. The cohesiveness is the ratio of the compression work expended in the second cycle to that in the first.

Gels Based on Cellulose Derivatives

The results of the texturometric analysis are given in Table 4 and Fig. 2.

Whether the type of cellulose derivative studied was HEC or HPC, and whether the consistency of the gel was semi-fluid or semi-stiff, all the different formulations presented similar values of cohesiveness [Fig. 2(a)], between 0.8 and 1.1.

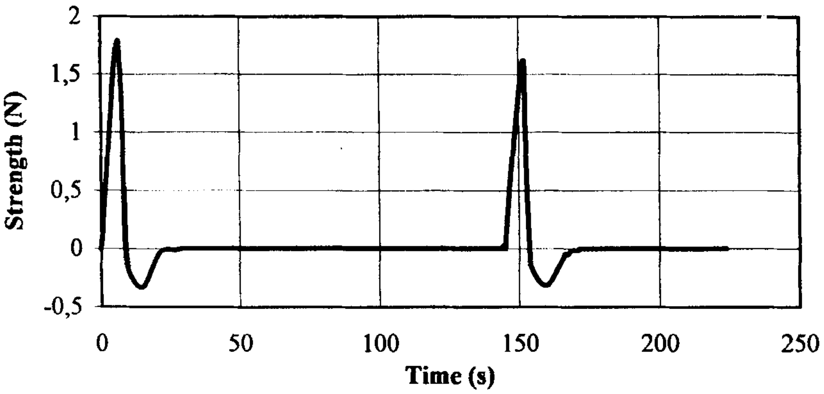

Figure 1. Texturometric analysis of gels: example of a graphical representation of a two-cycle study.

The stiffness values of the three semi-fluid gels (formulations 1, 3, and 5), each with a spreading diameter close to 60 mm, were almost identical (0.2 N). They were higher for the three semi-stiff gels with spreading diameters between 47 and 49 mm (formulations 2,4, and 6) [Fig. 2(b)].

The elasticities of the semi-fluid gels were very favorable (≥ 1).

The stiffest gels, classified semi-stiff, presented the highest adhesiveness values. The best results were obtained with formulation 6 containing 2.5% Klucel 98 HF-EP.

Gels Based on Carraghenates

Table 5 and Fig. 3 give the results of the texturometric analysis of the gels based on carraghenates with and without added K^+ or Na^+.

For gels containing carraghenates alone (formulations 7–10), the findings were as follows:

These gels were less cohesive than the cellulose-based gels.

The two semi-fluid gels (formulations 7 and 9), with spreading diameters close to 60 mm, had similar stiffness values, between 0.5 and 0.6 N. The semi-fluid cellulose-based gels, with equivalent spreading capacities, were half as stiff. Stiffness increased strongly for semi-stiff gels with spreading diameters of 43 and 44 mm (formulations 8 and 10, respectively).

The elasticity of all the gels (approx. 1) was very favorable.

Adhesiveness depended on the carraghenan concentration; the stiffest gels, classified semi-stiff, were the most adhesive.

The influence of Na^+ and K^+ on the texturometric characteristics of the carraghenate gels can be summarized as follows.

The cohesiveness of the semi-fluid gels based on Satiagel CT 52 was slightly increased in the presence on

Table 4

Texturometric Analysis of Gels Based on Cellulose Derivatives

Formulation No.	Cohesiveness	Stiffness (N)	Elasticity	Adhesiveness (mJ)
1	0.82204	0.18957	1.15690	2.2733
2	1.18000	0.31412	0.81700	5.9800
3	0.93263	0.19796	1.03510	2.5254
4	1.01320	0.29478	0.60825	5.2061
5	0.94920	0.20205	0.95161	3.7196
6	1.09050	0.36487	0.95161	6.5297

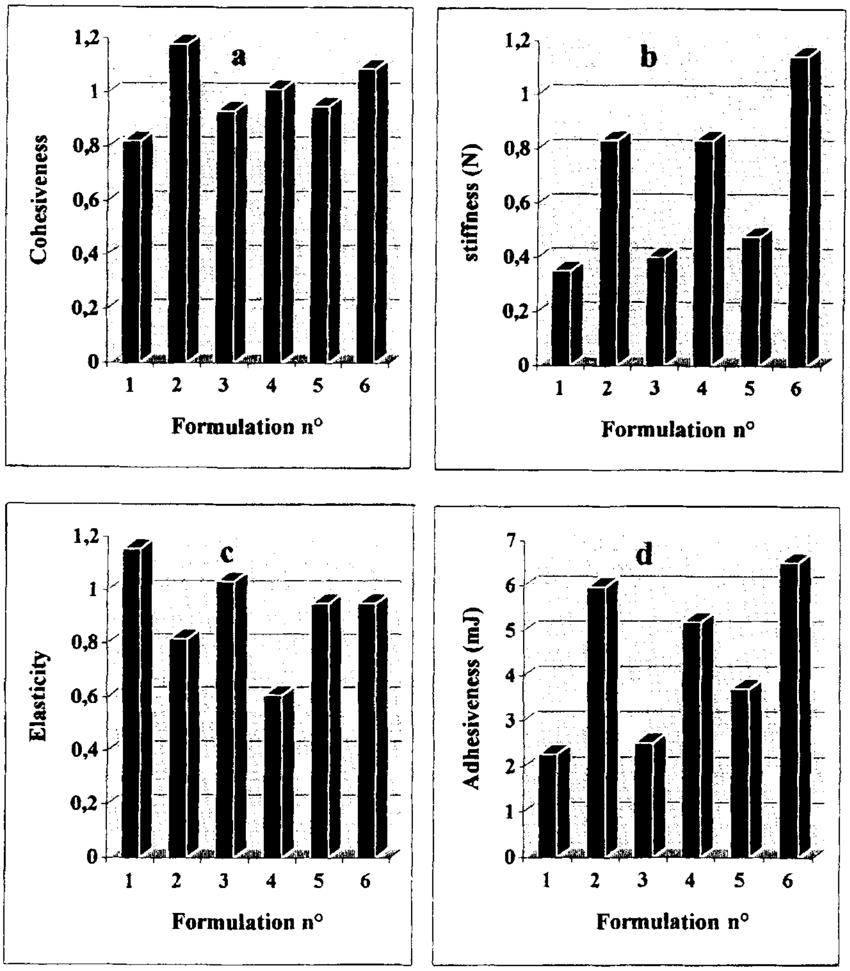

Figure 2. Texturometric analysis of gels based on cellulose derivatives. (a) Cohesiveness; (b) stiffness; (c) elasticity; (d) adhesiveness.

Table 5

Texturometric Analysis of Gels Based on Carraghenates

Formulation No.	Cohesiveness	Stiffness (N)	Elasticity	Adhesiveness (mJ)
7	0.61575	0.52172	1.07140	2.68570
8	0.74045	2.03700	1.01720	3.43910
9	0.69339	0.59121	1.05360	1.90870
10	0.52493	3.91950	1.03510	2.62520
11	0.85208	0.71517	1.0351	0.93035
12	0.10480	3.61930	0.98333	0.62920
13	1.38600	4.2670	1.01690	0.62328
14	0.60610	7.20620	1.00000	0.66600

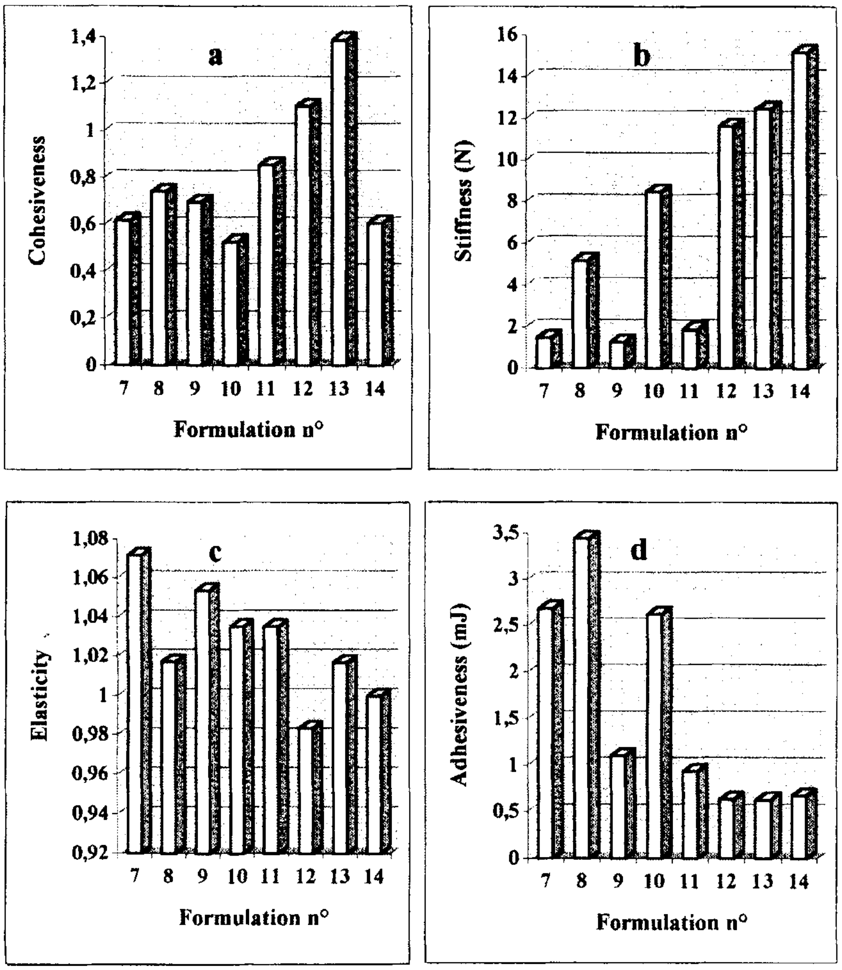

Figure 3. Texturometric analysis of gels based on carraghenates. (a) Cohesiveness; (b) stiffness; (c) elasticity; (d) adhesiveness.

Na^+ (formulation 11). It was more than doubled with K^+ (formulation 13). With the semi-stiff gels, addition of ions, especially Na^+ (formulation 12) also improved cohesiveness.

Unlike Na^+, K^+ strongly increased the stiffness of the gels. Among the semi-fluid gels, with spreading diameters close to 60 mm, the gel associating Satiagel CT 52 and potassium citrate (formulation 13) was seven times stiffer than that based on carraghenate alone.

The gels combining carraghenates and Na^+ or K^+ were less elastic than those based on carraghenates alone.

The presence of ions adversely affected adhesiveness; formulations 11 to 14 were four to five times less adhesive than formulations 9 and 10.

Gels Based on Alginates

The results of the texturometric analysis of gels based on alginates associated or not with Ca^{++} are given in Table 6 and Fig. 4.

For the gels based on alginates alone, the findings were as follows.

The cohesiveness of the gels based on sodium alginate (formulations 15 and 16) or potassium alginate (formulations 19 and 20) was highly satisfactory, and increased with concentration. The cohesiveness of the gels containing added Ca^{++} was less favorable, especially at the highest concentration (formulations 23 and 24).

Stiffness was low for the gels based on sodium or potassium alginate; for the same spreading diameter, the gels containing Ca^{++} were appreciably stiffer.

Table 6

Texturometric Analysis of Gels Based on Alginates

Formulation No.	Cohesiveness	Stiffness (N)	Elasticity	Adhesiveness (mJ)
15	1.01560	0.19214	1.07270	2.6703
16	1.16440	0.27855	0.79730	5.4744
17	0.96162	0.23081	1.05360	2.5762
18	0.76226	1.29200	1.03510	2.3447
19	0.78900	0.19982	1.13460	2.5319
20	1.15440	0.35001	1.03510	8.7329
21	0.86286	0.39633	1.00000	1.6314
22	0.86729	1.25140	1.00000	1.9513
23	0.72292	0.73273	0.98333	1.043
24	0.55551	3.0690	1.05360	2.1499

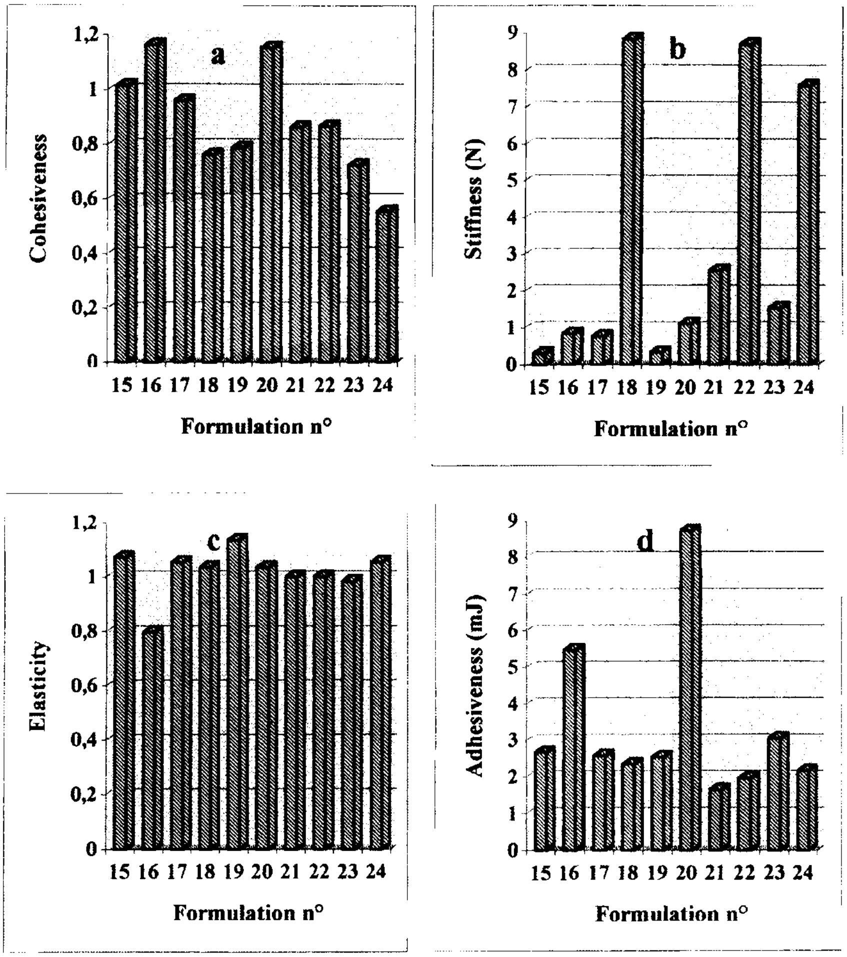

Figure 4. Texturometric analysis of gels based on alginates. (a) Cohesiveness; (b) stiffness; (c) elasticity; (d) adhesiveness.

All the gels had similar favorable elasticities.

The adhesiveness of the gels based on sodium or potassium alginate increased with the concentration of gelling agent; the opposite trend was observed with the sodium–calcium mixed alginate.

The texturometric analysis of the gels combining alginates and calcium gluconate (formulations 17, 18, 21, and 22) can be summarized as follows. Cohesiveness remained high but fell for the semi-fluid gels.

Ca^{++} did not affect the stiffness of the semi-fluid gels, but markedly increased that of the semi-stiff gels.

Ca^{++} had no significant effect on elasticity.

Ca^{++} reduced the adhesiveness of the semi-stiff gels (formulations 18 and 22). Its influence on the adhesiveness of the semi-fluid gels was much less marked.

CONCLUSION

The elasticity of the semi-fluid and semi-stiff gets varied little according to the gelling agent tested and is therefore not a discriminating factor.

For equivalent spreading diameters, the gels based on cellulose derivatives and those based on sodium or potassium alginate were much less stiff than the gels based on carraghenates. The stiffness of alginate-based gels was increased by adding Ca^{++} and that of the carraghenate-based gels was markedly enhanced by K^{+}.

All the gels had similar cohesiveness except for those based on carraghenates alone, which were less cohesive.

Figure 5 shows the influence on adhesiveness of the nature of the gelled vehicle and of its classification as semi-fluid or semi-stiff. The different formulations were ranked on a scale from 0 to 100 relative to the most adhesive gel taken as reference (100% adhesiveness).

The highest adhesiveness values were found among the semi-stiff gels. The five most adhesive gels were based on either sodium or potassium alginate, or cellulose derivatives. The strongest adhesiveness was obtained with 4% Kelmar potassium alginate (formulation 20).

The other four hydrogels were 25–40% less adhesive. These were, in older, formulation 6 based on highly polymerized HPC (Klucel 98 HF-EP 2.5%),

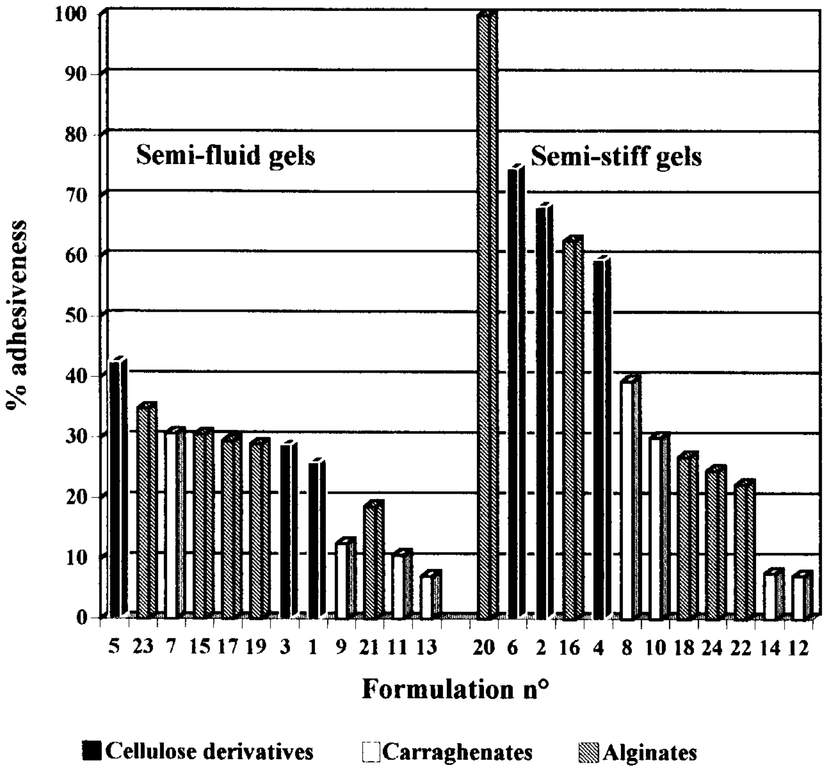

Figure 5. Classification of semi-fluid and semi-stiff gels according to their adhesiveness.

formulation 2 based on HEC (Natrosol 250G pharm 8%), formulation 16 based on sodium alginate (Satialgine S1600 3.5%), and formulation 4 based on moderately polymerized HPC (Klucel 99 MF-EP 3%).

All the other gels, whether semi-stiff or semi-fluid, were 2–10 times less adhesive than that of the reference gel based on potassium alginate. The least satisfactory results were obtained with the formulations associating carraghenates and Na^+ or K^+ (formulations 11, 12, 13, and 14).

ACKNOWLEDGMENTS

The authors thank Paul Legret for his technical collaboration.

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