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RESEARCH PAPER

Functionalization of Hydrocolloids: Principal Component Analysis Applied to the Study of Correlations Between Parameters Describing the Consistency of Hydrogels

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ABSTRACT

This work was part of a pure research project on the functionalization of three families of hydrocolloids: cellulose derivatives, carrageenates, and alginates. Principal component analysis (PCA), a powerful statistical method, was used to demonstrate the relations existing among these different parameters that describe the consistency of hydrogels and their spreadability. This approach therefore provides a basis for modeling hydrogel consistency. PCA also afforded a classification of hydrogels that demonstrated the remarkable adhesiveness of very stiff gels based on cellulose derivatives and sodium or potassium alginates. The corresponding semifluid gels and all the gels based on carrageenates and mixed sodium-calcium alginates, whatever their spreadability, were found to be very poorly adhesive. Generalized to all the many colloids currently marketed, this approach can be used to set up a databank for the formulation of mucoadhesive excipients.

Key Words: *Adhesiveness; Consistency; Hydrocolloids; Hydrogels; Texturometric analysis.*

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INTRODUCTION

For several years, we have been working on the study of numerous hydrocolloids currently on the market: cellulose derivatives, carrageenates and alginates (1). More important, it has prepared the ground for a pure research project on the functionalization of hydrocolloids on the basis of discriminating parameters, evaluated by fully validated methods such as rheology, the measurement of spreadability developed previously, and texturometric analysis (2). This last method is a promising tool for an instrumental approach to the sensory property represented by the texture because it quantifies cohesiveness, elasticity, and adhesiveness.

This research thus had a double purpose: (*a*) to complete the specification of the different colloids by setting up a data bank for mucoadhesive formulations and (*b*) to model the consistency of the hydrogels by establishing the correlations that link the different parameters involved. This paper presents the first results of this correlation study, carried out using principal component analysis (PCA), a powerful statistical tool for multivariate factorial analysis.

EXPERIMENTAL

Materials

The following gelling agents were tested: the cellulose derivatives hydroxyethylcelluloses (HECs) (Natrosol 250 G pharm® [Aqualon, Rue i Malmaison, France] and Tylose H 10000 P® [Clariant, Wiesbaden, Germany]) and hydroxypropylcelluloses (HPCs) (Klucel 99 MF-EP® and Klucel 98HF-EP® [Aqualon]); the carrageenates (Systems Bio-Industries, Boulogne, France) Satiagum UTC 10® and Satiagel CT 52®; the alginates sodium alginate Satialgine S1600® (Systems Bio-Industries) and potassium alginate Kelmar® (Kelco, Surrey, UK) and sodium-calcium alginate Kelset® (Kelco).

Methods

Preparation of Hydrogels

The gelling agents were dispersed in water containing 0.15% (w/w) Nipagine®, using an IKA RW20 DZM stirrer (Prolabo, Fontenay sous Bois, France). The dispersion was carried out at 20°C for the cellulose derivatives and alginates and at 35°C for the carrageenates. The stirring rate was set at 500 rpm.

Determination of Spreadability

The spreadability of the hydrogels was evaluated at 21°C ± 0.5°C 48 hr after preparation in the following conditions: The spreading diameter $\varnothing$ 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) according to the protocol previously validated (1). In these conditions, the following classification was adopted: fluid gel $\varnothing > 70$ mm, semifluid gel $70 \geq \varnothing > 55$ mm, semistiff gel $55 \geq \varnothing > 47$ mm, stiff gel $47 \geq \varnothing > 40$ mm, and very stiff gel $\varnothing \leq 40$ mm.

Rheological Study

The rheological study was carried out at 21°C ± 0.5°C with a Brookfield RVTD V2 viscometer equipped with the small adapter SC428/13R.

Texturometric Analysis

The texturometric analysis was carried out at 21°C using an Etia T04 texturometer equipped with a 50 N sensor. Each gel, packaged in 500-g containers, was analyzed in its original container without mixing or shaking. A two-cycle study was performed using the ‘‘cylindrical perforated plate’’ (diameter of the plate 70 mm, diameter of the perforations 7.4 mm) in the following conditions: speed of travel of the system 0.6 mm/sec; compression depth 4 mm; compression duration 6.7 sec; height of return between the two cycles 60 mm for the gel containing 10% Natrosol 250G and 40 mm for the other gels.

RESULTS

In each class of gelling agent and for each commercial product tested, we prepared four gelling vehicles with different consistencies: a semifluid gel with a spreading diameter of about 60 mm, a semistiff gel with a spreading diameter of about 50 mm, a stiff gel with a spreading diameter of about 45 mm, and a very stiff gel with a spreading diameter of about 37 mm (Table 1).

For each formula, seven parameters were measured. The spreading diameter (P1) of the hydrogels was evaluated using a method we developed and validated (1); P1 is considered to be an indicator of consistency. The two-cycle texturometric study quantified elasticity (P2), cohesiveness (P3), and adhesiveness (P4). Adhesiveness is the negative work (mJ) measured when the probe leaves the sample. The ratio of the compression durations of the first and second cycles determines the elasticity. Cohesion is

Table 1

Characteristics of the Hydrogels Tested

	HEC, Natrosol 250G				Highly Polymerized HEC, Tylose H10000P				HPC, Klucel 99MF-EP				Highly Polymerized HPC, Klucel 98HF-EP			
No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
C	5	6	7	10	2	2.4	3	4.5	2	3	3.5	6	1.5	2.5	2.8	3.7
P1	61	50	46	36	59	50	45	38	61	49	46	37	60	49	44	37
P2	1.16	0.88	0.85	0.68	0.97	0.89	0.42	0.68	1.04	0.61	0.39	0.55	0.95	0.95	0.44	0.48
P3	0.82	1.08	1.29	1.70	0.97	1.30	1.26	1.32	0.93	1.01	1.19	1.32	0.95	1.09	1.19	1.46
P4	2.27	3.12	4.59	15.9	2.51	5.68	9.67	11.4	2.53	5.21	9.13	17.6	3.72	6.53	9.39	15.6
P5	3.2	6.6	12.4	64.2	8.2	15.6	19	89.6	3.6	11.8	19.6	138	4.2	17.2	28	73.2
P6	1.21	1.21	1.21	1.32	1.28	1.31	1.41	1.72	1.42	1.67	1.73	1.73	1.14	1.43	1.46	1.66
P7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

	Carragheenates							
	With Middle % of κ and ι Fractions, Satiagum UTC10				With High % of κ and ι Fractions, Satiagel CT52			
No.	17	18	19	20	21	22	23	24
C	2.4	2.8	3	5	2	2.5	3	3.5
P1	62	50	43	37	61	51	44	37
P2	1.07	0.95	1.02	0.97	1.05	0.99	1.04	1.08
P3	0.62	0.75	0.74	0.90	0.69	1.01	0.52	0.82
P4	2.69	2.48	3.44	1.93	1.91	2.49	2.63	0.76
P5	9.8	17.6	22.6	57.6	7.6	48	69.2	106
P6	1.9	2.2	2.12	2.25	2.52	4.1	6.86	12.7
P7	<5	6.9	7.3	11.3	<5	14.3	41.1	12.4

	Alginates											
	Sodium Alginate Satialgine S1600				Potassium Alginate, Kelmar				Sodium/Calcium Alginate Kelset			
No.	25	26	27	28	29	30	31	32	33	34	35	36
C	2	3.5	4	6	2.5	3.5	4	5.2	1	1.5	1.7	2
P1	62	48	45	37	60	51	45	38	62	50	45	36
P2	1.07	0.8	0.67	0.77	1.13	0.81	1.03	0.7	0.86	1.01	1.01	1.03
P3	1.02	1.16	1.28	1.41	0.79	1.42	1.15	1.52	0.69	0.8	0.87	0.86
P4	2.67	5.47	6.89	18.1	2.53	10.4	8.73	22.3	2.4	1.38	1.45	0.89
P5	4.6	16.2	26	97.2	4	11.4	23.6	58.4	61.2	51.4	63.8	78.4
P6	1.26	1.25	1.22	1.24	1.35	1.61	1.83	1.55	5.16	3.37	2.7	2.06
P7	0	0	0	0	<5	<5	<5	<5	29.1	14.2	9.9	<5

Components: C, concentration % (w/w); P1, spreadability (mm). Texturometric parameters: P2, elasticity; P3, cohesiveness; P4, adhesiveness (mJ). Rheological parameters: P5, viscosity (mPa · s × 10^{-3}); P6, coefficient of pseudoplasticity; P7, thixotropy index.

defined as the ratio of compression work in the second cycle to compression work in first cycle. As concerns rheological parameters, in addition to the viscosity at 1 rpm (P5), the coefficient of pseudoplasticity N (P6) was calculated (3). The index of thixotropy $T_{\text{hyst\%}}$ (P7) was calculated by determining the area of the hysteresis loop as follows: After constructing ascending and descending rheograms, the difference $S_2 - S_1$ between the areas under the curves (S_1 = area under the ascending curve, S_2 = area under the descending curve) was calculated using Microcal® Origin 5.1 software (Northampton, MA):

$$T_{\text{hyst\%}} = 100 \times [(S_2 - S_1)/S_2]$$

Because the error in the measurement of areas S_1 and S_2 is due essentially to the standard error observed in the measurement of τ (i.e., at most 5%) (1), only the values of $T_{\text{hyst\%}}$ greater than 5 are considered significant. For all values less than or equal to 5, the gel is defined as nonthixotropic.

Results Obtained with Cellulose Derivatives

Table 1 confirms the positive correlation between concentration and degree of polymerization and between viscosity and nonthixotropicity of all the gels (1). Also, the coefficient of pseudoplasticity was practically independent of the type of substituent, the degree of polymerization, and the concentration. Concerning the texturometric parameters, adhesiveness was particularly discriminatory and increased with the concentration of the gelling agent.

Results Obtained with Carrageenates

Table 1 shows that the gelling power (viscosity), the coefficient of pseudoplasticity, and the thixotropy increased with the values of fractions κ and ι in the colloid. Overall, the gels based on carrageenates were less cohesive, more elastic, and, especially, much less adhesive than the cellulose-based gels.

Results Obtained with Alginates

As shown in Table 1, calcium ions considerably increase the viscosity and the coefficient of pseudoplasticity of hydrogels, but adversely affect their cohesiveness and adhesiveness. Also, unlike the formulations based on sodium or potassium alginate, gels based on mixed sodium-calcium alginates are thixotropic.

DISCUSSION

Although simple inspection of Table 1 enables us to draw certain general conclusions, the wealth of data hinders rapid assimilation of all the information they contain. A full interpretation of the results thus requires a powerful method of statistical analysis. We used factorial analysis, which uses the properties of Euclidian vector space to determine from statistical variables the maximum dispersion axes, which are mutually orthogonal, to identify fundamental structures of the complete set of statistical units. The method chosen here is principal component analysis (PCA) using the STAT-ITCF® software (4).

Initial Principal Components Analysis

Study of the Variables

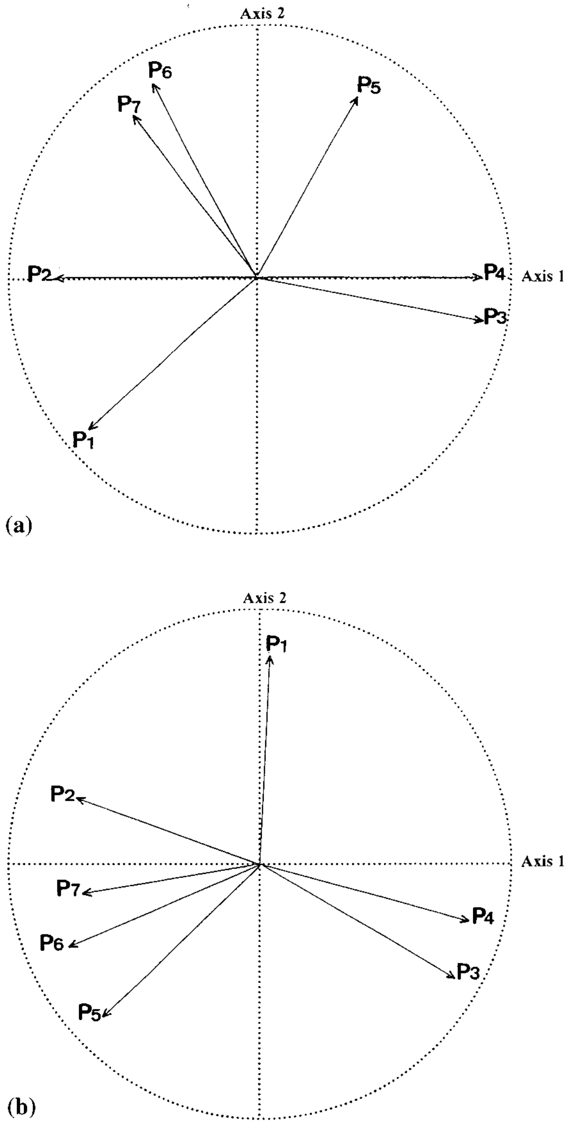

Figure 1. Principal component analysis circles of correlations in plane 1-2: (a) initial PCA (36 individuals, 7 variables); (b) additional PCA (24 individuals, 7 variables).

In the initial PCA (36 individuals and 7 variables), as shown graphically by the circle of correlations in plane 1-2 (Fig. 1a), the variables closest to axis 1 are adhesiveness (P4), elasticity (P2), and cohesiveness (P3), characterizing the texture of the hydrogels. The directions of the two variables P4 and P3 are opposite that of P2: as their elasticity decreases, the gels are more adhesive and more cohesive. Axis 2 is defined by the coefficient of pseudoplasticity (P6), the viscosity (P5), and the index of thixotropy (P7), characterizing the rheology. These three variables vary in the same direction. The spreading diameter (P1), well represented on plane 1-2, contributes equally to axis 1 and axis 2. The spreadability of the hy-

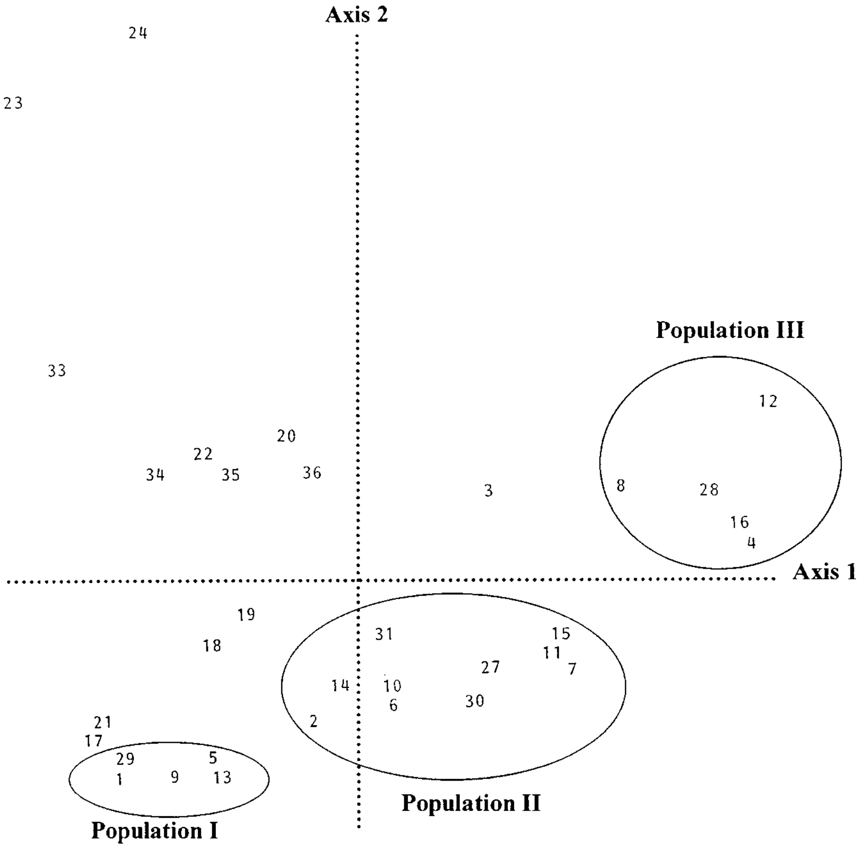

Figure 2. Initial PCA (36 individuals and 7 variables): graphical representation of the individuals in plane 1-2.

drogels thus depends on both their texture and their rheology.

Study of Individuals

The graphical representation of the individuals in plane 1-2 (Fig. 2) differentiates three populations, which we compare successively according to their positions relative to axis 1 (texture axis) and axis 2 (rheology axis).

Population I groups the semifluid gels, of about 60-nm spreading diameter, based on cellulose derivatives and sodium and potassium alginates. In terms of texture, these are the most elastic, the least adhesive, and the least cohesive gels. Rheologically, they are the least viscous and have the lowest coefficients of pseudoplasticity. They are also all nonthixotropic.

Population III groups the very stiff gels, of spreading diameter less than 40 mm, based on cellulose derivatives and sodium and potassium alginates. Texturally, these are the least elastic, the most adhesive, and the most cohesive. Rheologically, they are the most viscous and have the highest coefficients of pseudoplasticity. They are nonthixotropic, unlike the very stiff carrageenate-based gels, which are not included in this population.

Population II groups all the semistiff and stiff gels, of spreading diameter about 50 and 45 mm, respectively, based on cellulose derivatives and sodium and potassium alginates. Texturally, they are intermediate between populations I and III. Rheologically, they have low viscosity and low coefficients of pseudoplasticity, bringing them close to population I; they are all nonthixotropic.

This initial PCA thus enabled us to classify all the gels based on cellulose derivatives and sodium and potassium alginates.

Additional Principal Components Analysis

An additional analysis (24 individuals, 7 variables) was carried out to group the individuals not classified above, that is, the gels based on carrageenates and mixed sodium-calcium alginates. This additional analysis did not include the semifluid and very stiff gels based on cellulose derivatives and sodium and potassium alginates, which are properly grouped in populations I and III. However, population II, which was less homogeneous, was integrated in this additional analysis, which therefore concerned 24 individuals.

Study of Variables

The circle of correlations on this plane (Fig. 1b) shows that all the variables are well represented. The five variables forming axis 1 are cohesiveness (P3), adhesiveness (P4), elasticity (P2), coefficient of pseudoplasticity (P6), and index of thixotropy (P7): This axis is the texture and rheology axis. The most cohesive and most adhesive gels are the least elastic, have the lowest coefficients of pseudoplasticity, and are the least thixotropic. Axis 2 comprises only the spreading diameter (P1). The viscosity (P5) contributes equally to axis 1 and axis 2.

Study of Individuals

The graphic representation of the individuals on plane 1-2 (Fig. 3) differentiates four homogeneous groups, which we compare according to their positions relative to axis 1 (texture-rheology axis) and relative to axis 2 (spreadability).

- Goup A is identical to population II, comprising semistiff and stiff gels based on cellulose derivatives and sodium and potassium alginates. However, here it can be clearly subdivided, on the basis of spreadability, into two homogeneous subgroups, A1 (semistiff gels) and A2 (stiff gels).
- The gels based on carrageenates and mixed sodium-calcium alginates differ from group A in texture-rheology. They are more elastic, have higher coefficients of pseudoplasticity, and are less adhesive and less cohesive.

Their distribution into three groups (B, C, D) is based on their spreadability. We can differentiate semifluid gels (group B), semistiff and stiff thixotropic (group C) gels, and very stiff gels (group D).

CONCLUSION

Most of the research on hydrocolloids has relied on the rheological analysis of gelled vehicles, and the evalu-

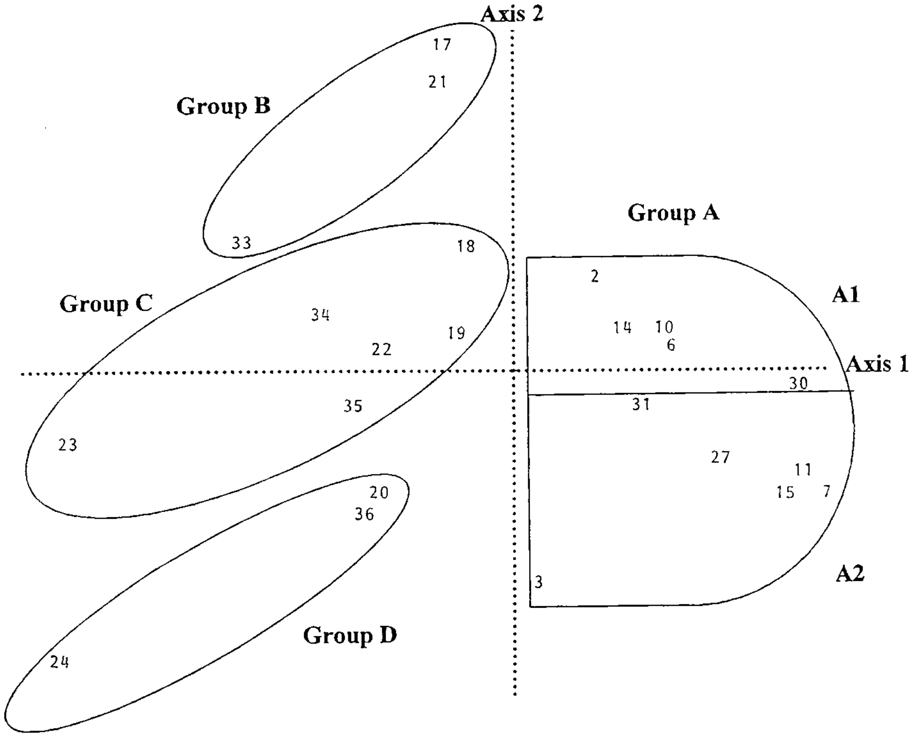

Figure 3. Additional PCA (24 individuals and 7 variables): graphical representation of the individuals in plane 1-2.

ation of the consistency of hydrogels is often reduced to viscosimetry (5,6). The work reported here shows that other physical parameters are highly relevant, especially spreadability and texturometric properties, as shown by the quality of the representation on the circle of correlations. PCA shows the relations that exist between these different parameters and the discriminating power of spreadability in hydrogel classification. This classification demonstrates the remarkable adhesiveness of very stiff gels based on cellulose derivatives and sodium and potassium alginates. In contrast, the corresponding semifluid gels and all the gels based on carrageenates and mixed sodium-calcium alginates, whatever their spreadability, were found to be very poorly adhesive. This approach should help to model hydrogel consistency and thereby attain better control over the formulation of mucoadhesive excipients.

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