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COMMUNICATIONS

PROCYANIDIN HYDROGELS. INFLUENCE OF CALCIUM ON THE GELLING OF ALGINATE SOLUTIONS

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ABSTRACT

Procyanidin hydrogels suitable for antacid therapy were developed from alginates with antipeptic properties. The influence of calcium ion on the gelling of colloidal solutions of sodium and potassium alginates was studied. Calcium gluconate displayed a marked reticulating ability, accentuating the pseudoplasticity and reducing the limpidity of the colloids.

INTRODUCTION

During work on the pharmaceutical uses of tannins (1) it was demonstrated that anti-ulcer activity of water soluble procyanidins obtained by fermentation of an extract of strawberry rhizomes was seen (2, 3). The development of procyanidins hydrogels, a drug dosage form suitable for anti-acid therapy was recently undertaken. The results of gel formulation based on cellulose and carrageenan derivatives have been reported (4, 5).

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The preparation and evaluation of alginate gels are studied here. Like the carrageenans, these colloids possess valuable antipeptic properties that justify their use in anti-ulcer treatments. It was of particular interest that the influence of calcium ion on the gelling of the colloidal solutions of sodium and potassium alginate tested was signified.

MATERIAL AND METHODS

Raw Materials

The following alginates were tested : Satialgine S 1100®, Satialgine S 1600® (Sanofi Bio-Industries) ; Texamid 778® (Henkel) ; Kelmar improved® , Kelset® (Kelco).
Calcium gluconate was used as the reticulating agent.

The procyanidins incorpored into the gels were prepared in these laboratories (6).

Methods

Preparation of Gels

The gelling agent was dispersed in water with an IKA RW20 helical stirrer at 20°C. The stirring rate was 500 r.p.m.

Determination of Spreadability

One gram of gel which was 24 hours old was pressed between two horizontal plates 20 cm square, of which the upper plate weighed 125 g and its diameter was measured against time (4).

Evaluation of Opalescence

The opalescence of the gels was studied using the method described in the French Pharmacopoeia (7), and spectrophotometric measurements of the transmission at 610 nm of reference solutions and the test gels were determined.

Rheological Study

A rheological study of the procyanidin gels was carried out at ambiant temperature (21°C) using a brookfield RVTD V_2® instrument fitted with an SC_4-28/13R small adapter.

RESULTS AND DISCUSSION

Thirty-three colloid and gelled vehicles were prepared containing 0.15 % Nipagine® with different types and concentrations of alginates and with and without added calcium gluconate.
Four of the products tested were basic alginates : sodium alginate (Satialgine S1100®, Satialgine S1600®, Texamid 778®), potassium alginate (Kelmar improved®) . Calcium ion has a reticulating action on alginate networks through the formation of aggregates. Gels may be obtained with a moderately substituted sodium/calcium alginate such as Kelset® (8).
Therefore, attention was directed to the influence of calcium gluconate on the gelling of the colloids studied.

Influence of the nature and concentration of alginates

As shown in Table 1, all the formulations tested had a pH close to 9, i.e. suitable for anti-ulcer therapy. Measurement of the spreading capacity of the different sodium alginate-based colloidal solutions showed the Satialgine® products to be best. They were more viscous solutions than potassium alginate.
In all, twelve formulations with satisfactory consistencies were obtained, nine based on sodium alginate (n°s 2 to 5, 7 to 9, 12 and 13) and three based on potassium alginate (n°s 14 to 16).

As shown in Table 2, all the preparations based on Texamid 778® and Kelmar improved® were weakly opalescent, while most of those containing Satialgine® were markedly so. Three formulations were finally accepted : n°s 7, 12 and 15. A rheological study of these colloids showed them to be pseudoplastic and thixotropic.

Influence of calcium gluconate on the gelling of alginate solutions

The influence of calcium gluconate on the gelling was studied for three colloidal alginate solutions with similar spreading diameters (approximately 70 mm) : n°6 with 1.5 % Satialgine S1600®,

TABLE 1

Procyanidin Gels based on Alginates. pH and Spreadability

Type of alginate	Gelling agent	Concentration (w/w)	pH	Spreading diameter after 1 min (mm)	Formulation n°
Sodium alginate	Satialgine® S 1100	1.5	9.3	81	1
		2	9.3	65	2
		2.5	9.3	62	3
		3	9.3	57	4
		4	9.1	50	5
	Satialgine® S 1600	1.5	9.3	71	6
		2	9.3	61	7
		2.5	9.2	55	8
		3	9.2	51	9
	Texamid® 778	1	9.3	101	10
		2	9.3	74	11
		3	9.3	60	12
		3.5	9.2	50	13
Potassium alginate	Kelmar improved®	2	9.1	70	14
		2.5	9.15	62	15
		3	9	56	16
		3.5	9	49	17

TABLE 2

Procyanidin Gels based on Alginates. Assessment of Limpidity

Gelling agent	Concentration (w/w)	T % at 610 nm	Formulation n°
Satialgine S 1100®	2	28	2
	2.5	27	3
	3	26	4
	4	22.5	5
Satialgine S 1600®	2	42	7
	2.5	39.5	8
	3	36.5	9
Texamid 778®	3	67	12
	3.5	55.5	13
Kelmar improved®	2	68	14
	2.5	59	15
	3	52.5	16

n°11 with 2 % Texamid 778 ® and n°14 with 2 % Kelmar improved®. The characteristics of the 12 formulations tested are collected in Tables 3 and 4. These tables also include the results obtained in the formulation of reference gels based on moderately substituted sodium/calcium alginate (Kelset ®).

As above, all the gels had an appreciably basic pH, close to 9, i.e. compatible with anti-ulcer therapy. The two selection criteria, spreading diameter and percentage transmission at 610 nm, showed Kelset ® to be a remarkably good gelling agent. They also served to evaluate the influence of calcium gluconate on the gelling of the basic alginate solutions tested.

For simplicity, six representative formulations of colloids and alginate-gluconate gels will be considered ; their caracteristics are compared in Table 5.

The influence of calcium gluconate was studied for three colloidal solutions of alginates with similar spreading diameters ($\geqslant$ 70 mm), n°6 with 1.5 % Satialgine S1600 ®, n°11 with 2 % Texamid 778® and n°14 with 2 % Kelmar improved® .

The results in Table 5 confirm the reticulating power of calcium gluconate towards sodium and potassium alginates. The fluid colloidal solution with 1.5 % Satialgine S1600 ® displayed a spreading diameter of 71 mm (formulation n°6). The addition of 0.18 % calcium gluconate produced a gel with a spreading diameter of 57 mm (formulation n°20).

Likewise, formulation n°28 with 2 % Kelmar improved® and 0.15 % calcium gluconate displayed a spreading diameter of 61 mm against 70 mm for the corresponding calcium-free colloid.

A rheological study of these different formulations also showed that the addition of calcium gluconate accentuated the pseudoplaticity of the preparations.

The addition of calcium gluconate reduced the limpitidy of the gels ; however, values of T % at 610 nm were still satisfactory, i.e. over 42 %, the value below which the preparation is considered opalescent (4).

TABLE 3

Procyanidin Gels based on Alginates.

Influence of Calcium Gluconate on pH and Spreadability

Type of alginate	Gelling agent % (w/w)	Calcium gluconate % (w/w)	pH	Spreading diameter (mm)	Formulation n°
Sodium alginate	Satialgine S 1600 ® 1.5 %	0.1	9.3	71	18
		0.15	9.4	67	19
		0.18	9.4	57	20
		0.2	9.4	52	21
	Texamid 778 ® 2 %	0.15	9	70	22
		0.2	9.1	68	23
		0.25	9.1	61	24
		0.3	9.1	50	25
Potassium alginate	Kelmar improved ® 2 %	0.05	9	67	26
		0.1	9	65	27
		0.15	9	61	28
		0.2	9	55	29

Type of alginate	Gelling agent	Concentration % (w/w)	pH	Spreading diameter (mm)	Formulation n°
Sodium-calcium alginate	Kelset®	0.75	9	78	30
		0.8	9	66	31
		0.9	9	62	32
		1	9	56	33

TABLE 4

Procyanidin Gels based on Alginates.

Influence of Calcium Gluconate on Limpidity

Gelling agent % (w/w)	Calcium gluconate % (w/w)	T % at 610 nm	Formulation n°
Satialgine S 1600 ® 1.5 %	0.15	67	19
	0.18	43	20
	0.2	33	21
Texamid 778 ® 2 %	0.15	80.5	22
	0.2	79	23
	0.25	72	24
	0.3	66	25
Kelmar improved® 2 %	0.05	79	26
	0.1	71	27
	0.15	64	28
	0.2	41	29

Gelling agent	Concentration % (w/w)	T % at 610 nm	Formulation n°
Kelset®	0.8	57	31
	0.9	54	32
	1	45	33

TABLE 5

Influence of Calcium Gluconate on the Gelling of three Colloidal Solutions of Alginates

Gelling Agent	Concentration % (w/w)	Calcium Gluconate % (w/w)	Spreading diameter after 1 min. (mm)	T % at 610 mm	Formulation n°
Satialgine S 1600®	1.5	-	71	52	6
	1.5	0.18	57	43	20
Texamid 778®	2	-	74	77	11
	2	0.25	61	72	24
Kelmar improved®	2	-	70	68	14
	2	0.15	61	64	28

Hence, the study of the influence of calcium gluconate on gelling produced three gel formulations with particularly favorable consistencies and limpidities ; n°19 with 1.5 % Satialgine S1600® and 0.15 % calcium gluconate, n°23 with 2 % Texamid 778® and 0.2 % calcium gluconate, and n°26 with 2 % Kelmar improved® and 0.05 % calcium gluconate.

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REFERENCES

1. B. Vennat, "Proanthocyanidines : obtention par voie fermentaire et préparation de divers complexes", Thesis Doct. Pharm., Clermont-Ferrand, 1985.

2. B. Vennat, A. Pourrat, H. Pourrat, D. Gross, P. Bastide, J. Bastide, Chem. Pharm. Bull., 36, 2, 828 (1988).

3. B. Vennat, D. Gross, H. Pourrat, A. Pourrat, P. Bastide, J. Bastide, Pharm. Acta Helv., 64, 11, 316 (1989).

4. B. Vennat, D. Gross, A. Pourrat, H. Pourrat, Drug Dev. Ind. Pharm., 17, 15, 2083 (1991).

5. B. Vennat, D. Gross, A. Pourrat, Drug Dev. Ind. Pharm., 18, 14, 1535 (1992).

6. B. Vennat, A. Pourrat, H. Pourrat, J. Ferment. Technol., 64, 3, 227-231 (1986).

7. Pharmacopée Française, Xe édition, Maisonneuve, Paris, 1983.

8. Kelco® documentation technique.