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RESEARCH PAPER

Development of Ointment Formulations Prepared with *Achyrocline satureioides* Spray-Dried Extracts

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ABSTRACT

Achyrocline satureioides *spray-dried extracts, prepared with colloidal silicon dioxide, microcrystalline cellulose + colloidal silicon dioxide (1:1), and β-cyclodextrin + colloidal silicon dioxide (1:1), were incorporated in a glyceryl monostearate base. The influence of the spray-drying adjuvants on the formulations' physical characteristics, such as spreading properties, oil indexes, viscosities, and the pH determination, were evaluated. The results indicated that the adjuvants influenced the ointments' physical parameters at different levels, although all of them maintained their plastic flow and presented antithixotropic behavior. The presence of colloidal silicon dioxide alone, in the dried extract, imparted the lowest oil index value and an intermediary spreading area to the ointment. The colloidal silicon dioxide content reduction and the substitution of part of it by β-cyclodextrin or microcrystalline cellulose enhanced the ointments' oil index values, while the best spreading area was reached by the ointment prepared with the spray-dried extract containing colloidal silicon dioxide and microcrystalline cellulose.*

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INTRODUCTION

The plant known as "marcela" or "macela," *Achyrocline satureioides* (Lam.) DC. Compositae, is widely used in popular preparations in Southern South America. The topical anti-inflammatory activity of alcoholic extracts prepared with the plant inflorescences was confirmed in 1988 (1). Therefore, hydrophilic and lipophilic ointments were formulated by the incorporation of *A. satureioides* concentrated extract (2). The ethanolic extract, concentrated under vacuum, exhibited some disadvantages, such as low solubility in the ointment bases and a sticky aspect, which disturbed the extract handling. Thereafter, *A. satureioides* spray-dried powders were obtained (3,4) starting from low ethanol content extracts. Three different spray-drying adjuvant combinations were tested (4): colloidal silicon dioxide alone, admixtures of colloidal silicon dioxide + microcrystalline cellulose (1:1), and colloidal silicon dioxide + β-cyclodextrin (1:1), resulting in physically different powders.

This paper presents the development of three ointments, by the incorporation of the three spray-dried combinations in a unique base, and evaluates the formulations from physical and physicochemical viewpoints. The viscosity, spreading properties, and oil index determinations were used to reveal any differences among the three ointments, possibly imparted by the presence of the different drying adjuvants.

EXPERIMENTAL

Materials and Methods

Spray-Dried Extracts

The *A. satureioides* spray-dried powders were prepared from extracts obtained by the maceration of 7.5% inflorescences (w/v) in ethanol 80% (v/v) (5). Polysorbate 80 (Merck) and the drying excipients colloidal silicon dioxide (Aerosil 200 Degussa); microcrystalline cellulose (Avicel PH 101, FMC) + colloidal silicon dioxide (1:1); and β-cyclodextrin (Merck) + colloidal silicon dioxide (1:1) (Table 1) were added to the ethanolic extracts and the mixtures were concentrated under vacuum to half of their original weight. The drying process was performed in a mini spray-dryer 190 (Büchi) with a pneumatic atomizer and concurrent flow at a feed speed of 3 ml/min, with an inlet temperature of 150–160°C, and outlet temperature of 95–96°C. The final spray-dried powders were labeled SD1, SD2, and SD3, respectively (4). Their composition is shown in Table 1.

Glyceryl Monostearate Base (GMS)

The base was prepared according to the normal preparation technique for emulsions. The isolated hydrophilic and hydrophobic phases were heated to 70°C, then were gently stirred in an Erweka PRS planetary mixer. The composition of the GMS base is reported in Table 2.

Ointments

The ointments were prepared in mortars and pestles, by the incorporation of 0.2 g of each spray-dried powder SD1, SD2, and SD3 per gram of the GMS base. The resulting formulations were termed O1, O2, and O3, respectively. The GMS base and the ointments were analyzed 2 days after preparation.

Ointment Analysis

pH Determination

The GMS base and the ointments O1, O2, and O3 were diluted to 10% (m/v) in distilled water and their

Table 1

Composition of the Achyrocline satureoides *Spray-Dried Extracts (SD)*

Components	Spray-Dried Extract		
(g)	SD1	SD2	SD3
A. satureoides 80% ethanol extract	100.0	100.0	100.0
Polysorbate 80	0.35	0.35	0.35
Colloidal silicon dioxide	1.40	0.70	0.70
Microcrystalline cellulose	–	0.70	–
β-cyclodextrin	–	–	0.70
Water	80.0	80.0	80.0

Table 2

Composition of the Glyceryl Monostearate Base (GMS) and Ointments O1, O2, and O3, Prepared by the Incorporation of Spray-Dried Extracts

Components	Amount (g)
Stearic acid	3.30
Sorbic acid	0.10
Water	62.3
Lanolin	1.00
Glyceryl monostearate	6.20
Triethanolamine	1.40
Mineral oil	11.4
White petrolatum	14.3
α-Tocopherol	0.03
Ascorbyl palmitate	0.03
Spray-dried extract	20.0
Total	120.0

pH values were determined in a Digimed DMPH-2 potentiometer, at room temperature.

Spreading Test (6)

This method consisted of submitting a determined amount of sample, the ointment or the GMS base, to compression under several glass plates of known weight. Twenty plates were subsequently displayed over the sample: at 1-min intervals, the spreading area reached by the sample was measured, in millimeters, in the vertical and horizontal axis. The results were expressed as spreading area as a function of the applied mass (*i*), accordingly to Eq. (1).

$$Si = \frac{d^2 \cdot \pi}{4} \quad (1)$$

where Si is the spreading area (mm^2) resultant from the applied mass *i* (g), and *d* is the mean diameter reached by the sample (mm). The data were statistically evaluated by analysis of variance/one-way repeated measures (ANOVA/OWRM) and Student-Newmann-Keuls test.

Oil Index Determination (7,8)

The GMS base and ointment samples were mixed in mortars and pestles for 3 min. Afterward, known amounts of the samples were displayed on filter paper disks (12 cm diameter), previously weighed. The disks containing the samples were placed in an oven at 30°C for 24 hr. The oil released from the formulations was absorbed by the filter paper disks, creating oil rings around the samples. The GMS base and ointments were discarded and the disks were weighed a second time. The percent oil content liberated by the samples was calculated, corresponding to the mean of five repetitions. The results were statistically evaluated by ANOVA/OWRM and Student-Newmann-Keuls test.

Viscosity Determination

The samples' viscosities were measured in a Brookfield rotational viscometer, model SP Y3, at 25°C, with a shear rate interval from 5 to 50 rpm.

RESULTS AND DISCUSSION

The produced ointments showed a brilliant aspect and a homogeneous yellowish coloration. The spray-dried powders, SD1, SD2, and SD3, incorporated in the GMS base, caused a general decrease in pH values (Table 3). The lower pH value was detected for O2, which contained the spray-dried extract prepared with colloidal silicon dioxide + microcrystalline cellulose. Nevertheless, the pH values of all the ointments were compatible

Table 3

Physical and Physicochemical Data from the GMS Base and Ointments O1, O2, and O3

Sample	pH ± SD $n = 4$	Oil Index (% ± SD) $n = 5$	Spreading Area (mm^2) (min/max)[a] $n = 3$
O1	6.45 ± 0.16	20.91 ± 0.79	109.46/1361.14
O2	6.30 ± 0.16	30.28 ± 0.77	403.28/1537.89
O3	6.32 ± 0.19	28.12 ± 0.99	457.3/1352.65
GMS base	7.85 ± 0.13	16.49 ± 0.63	1075.2/2816.1

[a](min/max): Minimal and maximal spreading areas reached by the samples.

with the skin pH, which ranges from 4.5 to 6.5 depending on the body skin zone.

The oil index indirectly indicates the probability of breakdown of emulsion-like systems, presumably caused by the influence of some ingredients on the surfactant stability, eventually resulting in phase separation. The ointments' phase separation could be caused by the incorporation of the spray-dried extract into the GMS base. Moreover, the oil index value is influenced by the liquid phase viscosity. Table 3 reports oil indexes that are remarkably different between the ointments and the GMS base, for $\alpha = 0.05$. The oil indexes for O2 and O3 were considered different from O1 for the same significance level. The GMS base oil index was used as reference for the system stability analysis. The data in Table 3 show that O1 was the most stable of all formulations, since it manifested the lower oil index. This stability could be because this ointment spray-dried extract was prepared only with colloidal silicon dioxide, which could have enhanced the water phase viscosity, reducing the possibility of oil release from the system inner phase. The other two ointments, O2 and O3, contained only half of the colloidal silicon dioxide content of O1 and showed larger oil index values, but similar values between themselves.

The spreading test was applied to facilitate quality control of ointments, since spreading is an important characteristic for preparations designed for skin application. The ointments' spreading areas, reported in Fig. 1, were smaller than the value presented by GMS base. The incorporation of the spray-dried powders into the GMS base caused, on average, 50% decrease in the maximal spreading area reached by the base. The statistical analysis for the maximal spreading areas demonstrated that the data of O1 and O3 were similar for $\alpha = 0.05$ but O2 presented a higher value, statistically different for the same significance level. These data revealed that the spray-dried powders indistinctly altered the GMS base internal structure, increasing the base consistency. As a consequence, the ointments were considerably stiffer and had reduced spreading properties. The substitution of β-cyclodextrin in O3 by microcrystalline cellulose in O2 was responsible for improving the ointment spreading. Thus, it can be inferred that the drying adjuvant adopted in the spray-dried extracts increased the GMS base external phase viscosity, reducing the moving capacity of the layers while the formulations were spread. This reduction appeared to different extents according to the sort of adjuvant adopted, being larger when colloidal silicon dioxide alone, and colloidal silicon dioxide + β-cyclodextrin were used.

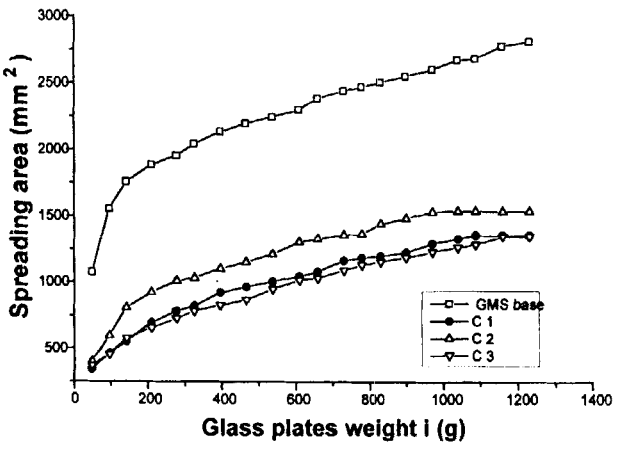

Figure 1. Spreading profiles for the glyceryl monostearate base (GMS) and for the ointments O1, O2, and O3.

In addition to the spreading test, the ointments' rheological behavior, more precisely their viscosity, was studied since products which are viscous enough to retard phase separation, but also fluid enough to permit pouring from a flask and spreading on the application site may be developed. The formulation viscosity is defined as the resistance to movement of the preparation molecules; a movement usually described as flow (10). The GMS base and the O1, O2, and O3 could be classified as non-Newtonian flow preparations, since their viscosities (η) were not constant, but changed as a function of the shear rate (D) [Fig. 2(a), Fig. 3(c), Fig. 4(e), and Fig 5(g)]. The rheograms in Fig. 2(b), Fig. 3(d), Fig. 4(f), and Fig. 5(h) also show that GMS base and the ointments are plastic materials, because they do not flow immediately after being submitted to a shear stress (τ). The values at which the formulations start flowing are called yield value (τ^0) and were calculated through NCA/CM CASSON as in Eq. (2):

$$(1 + a)\,\tau = 2\,(\tau^0) + (1 + a)\,(\eta' D) \qquad (2)$$

where τ is the shear stress (Pa); D is the shear rate (sec^{-1}), η′ is the plastic viscosity (mPa·sec), τ^0 is the yield stress (Pa), a is the ratio between r_2/r_1 (cm) (external and internal radius in the viscometer). The yield values (Table 4) indicate that the ointments maintained the GMS base plastic behavior, where O3 presented the highest resistance to start flow, followed by O1 and O2 showed the lowest resistance.

The slower the layers of a fluid move in relation to each other, by virtue of a shear stress, the greater is the fluid viscosity. Hence, the spray-dried combination microcrystalline cellulose + colloidal silicon dioxide +

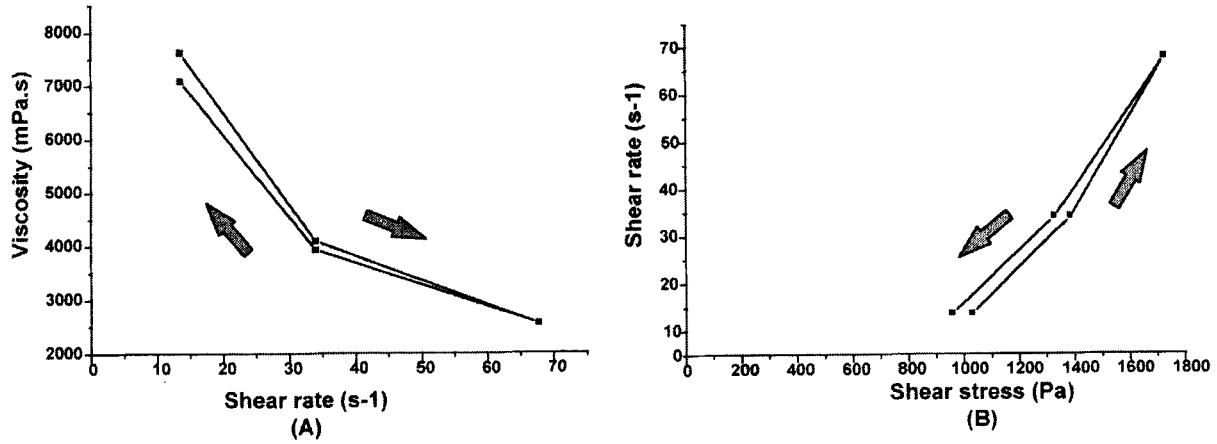

Figure 2. Glyceryl monostearate base rheograms showing the non-Newtonian behavior (a) and the thixotropic effect (b).

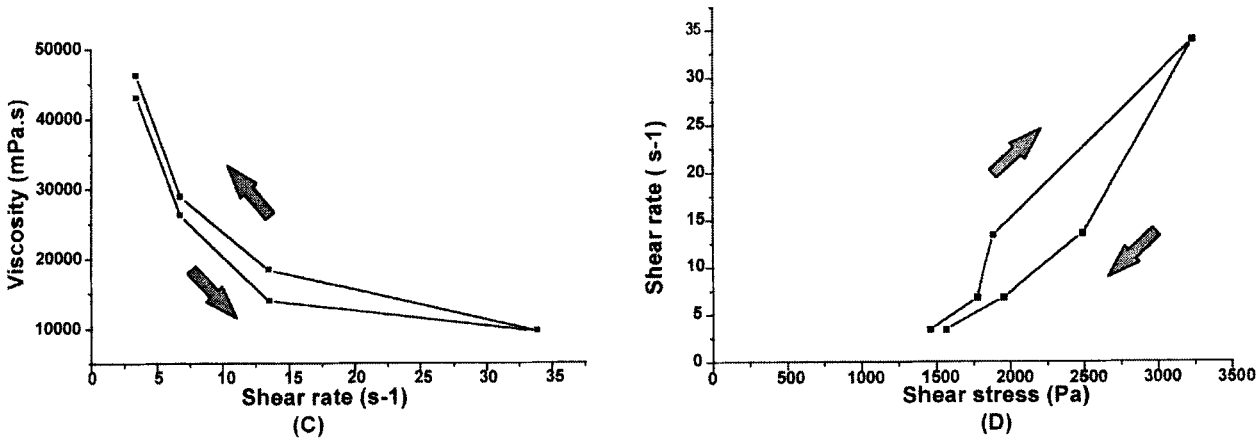

Figure 3. Ointment O1 rheograms showing the non-Newtonian behavior (c) and the antithixotropic effect (d).

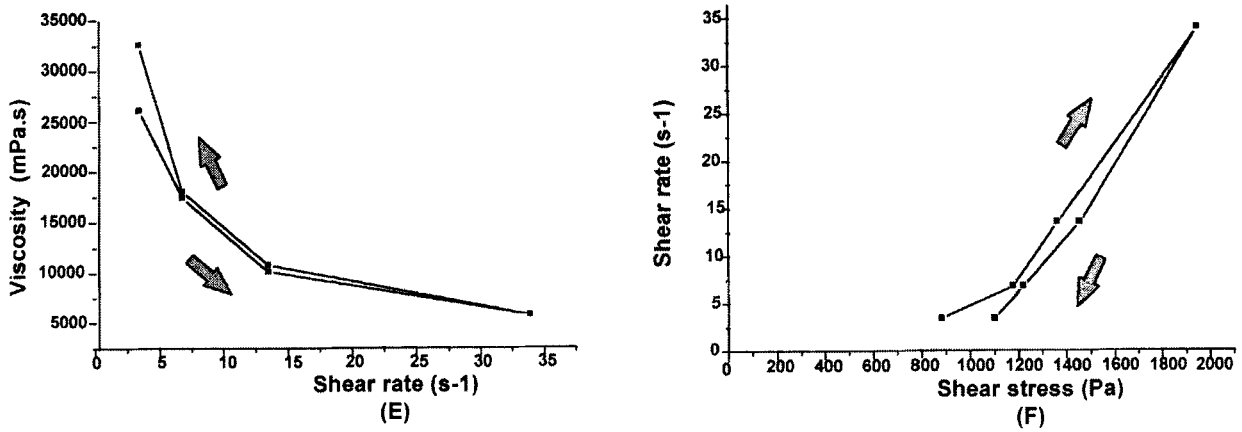

Figure 4. Ointment O2 rheograms showing the non-Newtonian behavior (e) and the antithixotropic effect (f).

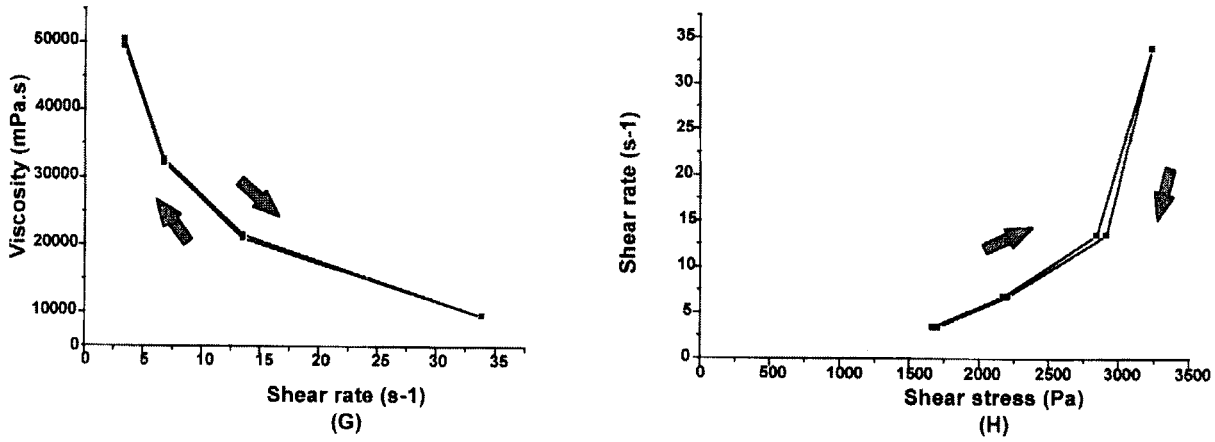

Figure 5. Ointment O3 rheograms showing the non-Newtonian behavior (g) and the nonsignificant antithixotropic effect (h).

the vegetable extractives influenced the ointment O2 flow. This solid extract represented the smallest barrier against the ointment layers shearing, and as a result, O2 showed the lowest viscosity among the other ointments, which corresponded with its spreading behavior.

The rheogram analysis indicates that the GMS base presents a thixotropic behavior, demonstrated by an anticlockwise histeresis loop [Fig. 2(b)]. Thus, the GMS base has a tendency to thin after being exposed to a shearing force, followed by a tendency to thicken when the stress is removed. As it can be seen in Fig. 3(d), Fig. 4(f), and Fig. 5(h), the ointments O1 and O2 showed a reversed effect, and their rheogram curves show a clockwise histeresis loop. This flow characteristic is described as an antithixotropic effect (9), and was not significant for O3. , The extension of the antithixotropic effect can be measured by the area between the ascendant and descendant curves. This phenomenon is usual for systems containing large amounts of solids, such as the ones presented in this paper. Thus, the ointments tend to thicken after being exposed, for a period of time, to a shear stress, followed by a tendency to thin after the stress is removed. The largest effect was observed in O1, whose extract, SD1, contains only colloidal silicon dioxide as drying adjuvant.

Table 4

Yield Values (τ^0) of the GMS Base and Ointments Calculated in Accordance with Eq. (2)

Sample	Yield Value (τ^0) (Pa)
GMS base	436.6
O1	807.7
O2	568.1
O3	1049.0

CONCLUSION

The incorporation of *A. satureioides* spray-dried extracts demonstrated to be more successful than the incorporation of other concentrated extracts, since they were easier to handle and presented greater solubility in the GMS base, producing homogeneous ointments.

The solid extracts' incorporation to the GMS base promoted an alteration into the retention of the internal phase by the external phase, since the GMS base is an oil/water (o/w) emulsion. Thus, after being submitted to a shearing stress, the formulation O2 was the most damaged and released the largest amount of oil. This result suggests that the adjuvant combination between colloidal silicon dioxide + microcrystalline cellulose (O2) was the mixture that notably disturbed the o/w interface stability, followed closely by the colloidal silicon dioxide + β-cyclodextrin combination (O3), when they are compared to the isolated colloidal silicon (O1). The latter seemed to act by increasing the emulsion outer phase viscosity, which improved the final ointments' stability against the shearing forces. Nevertheless, although it was proved that the drying adjuvant influenced the ointments' physical stability at different levels, none of them caused the ointments' emulsions to break down. The adjuvants also modified the spreading and the viscosi-

ties of the ointments, reducing their site application capacity, because of the higher consistency they imparted to the ointments. It was observed that the drying adjuvant which least reduced the ointment spreading ability was the combination between colloidal silicon dioxide + microcrystalline cellulose (O2), but the lowest antithixotropic effect was developed by the combination of colloidal silicon dioxide + β-cyclodextrin (O3). Since the latest formulation presented a similar spreading characteristic as the formulation containing only colloidal silicon dioxide (O1), it seems that the magnitude of the antithixotropic effect, which was highest for O1, but did not interfere with the formulations' spreading ability, even though all formulations presented plastic non-Newtonian behavior. The results indicate that for the GMS base and ointments, the viscosities tend to decrease as a function of the applied shearing force.

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