

## TOPICAL DOSAGE FORMS CONTAINING FLUIDEXTRACT OF *RUSCUS ACULEATUS*: FORMULATION, PREPARATION AND PHYSICAL CHARACTERIZATION

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### Abstract

**Objective.** In this paper we present the formulation, preparation and physical characterization of some topical dosage forms (gel, cream and suppositories) containing fluidextract of *Ruscus aculeatus*, designed for the treatment of hemorrhoidal disease.

**Methods.** The new formulations were prepared by specific methods. The semisolids preparations were analyzed regarding the homogeneity, spreading capacity, consistency and rheological properties. Homogeneity, resistance to rupture and disintegration were evaluated for suppositories. All the preparations were tested as fresh products and after one year storage at cool.

**Results.** The fresh gel and cream were homogeneous preparations, in accord with Romanian Pharmacopoeia X<sup>th</sup> ed. requirements. The suppositories quality was in accord with Romanian Pharmacopoeia X<sup>th</sup> ed. requirements concerning the homogeneity, the resistance to rupture and disintegration. The tested physical characteristics of gel and suppositories remained unchanged within the storage interval, whereas the consistency and the viscosity of the cream decreased.

**Conclusions.** The gel and the suppositories formulations were physically stable but the cream composition must be optimized in order to improve their physical stability.

**Keywords:** *Ruscus aculeatus*, topic preparations, suppositories.

## FORME FARMACEUTICE TOPICE CU EXTRACT FLUID DE *RUSCUS ACULEATUS*: FORMULARE, PREPARARE ȘI CARACTERIZARE FIZICĂ

### Rezumat

**Obiective.** În această lucrare este prezentată formularea, prepararea și caracterizarea fizică a unor forme farmaceutice topice (gel, cremă, supozitoare) cu extract fluid de *Ruscus aculeatus*, destinate tratamentului bolii hemoroidale.

**Metode.** Noile formulări au fost preparate prin metode specifice. Preparatele semi-solide au fost analizate din punct de vedere al omogenității, al capacității de întindere, al consistenței și al proprietăților reologice. În cazul supozitoarelor au fost testate omogenitatea, rezistența la rupere și dezagregarea. Toate produsele au fost evaluate imediat după preparare și după o perioadă de stocare de un an, la rece.

**Rezultate.** Crema și gelul, după preparare, au fost omogene, corespunzând cerințelor Farmacopeei Române ediția a X-a. Supozitoarele au corespuns cerințelor Farmacopeei Române ediția a X-a și Suplimentului din 2001 în ceea ce privește omogenitatea, rezistența la rupere și timpul de dezagregare. Gelul și supozitoarele s-au dovedit a fi stabile, păstrându-și nemodificate timp de un an proprietățile testate, în timp ce consistența și vâscozitatea cremei au scăzut.

**Concluzii.** Gelul și supozitoarele sunt stabile din punct de vedere fizic.

Compoziția cremei trebuie optimizată în vederea creșterii stabilității fizice.

**Cuvinte cheie:** *Ruscus aculeatus*, preparate topice, supozitoare.

## INTRODUCTION

*Ruscus aculeatus* L. (butcher's broom), member of the *Liliaceae* family, is known as medicinal plant by its rhizomes (*Rusci aculeati rhizoma*) that contain steroidal saponins, aglycons being ruscogenin and neoruscogenin with benefic antiinflammatory, vasotonic and antihemorrhoidal effects [1].

For therapy purposes the standardized extracts and the isolated pure active substances (ruscogenin and neoruscogenin), alone or associated with other substances or extracts with similar properties are used [2].

Extracts, capsules, tablets, ointments, suppositories obtained from *Rusci aculeati rhizoma* are currently found on the Romanian pharmaceutical market. These forms are comercialized under various names: Ruscoven® (ABOCA), Venelbin® (BIOCUR), Proctolog® (PFIZER), Varicosin® (PHYTO PHARMICA) etc.

The aim of the present study was to formulate and prepare gel, cream and suppositories formulations with fluidextract of *Ruscus aculeatus* and to test their physical properties in order to evaluate the products physical stability.

## MATERIALS AND METHODS

### Materials

The plant material was collected from Dorgos locality (Arad county, Romania) in October 2004. Carbopol 940 (B.P.Goodrich), triethanolamine (TEA) (Merck), cethylic alcohol (BASF), sodium laurylsulfate (Merck), fatty suppository base Suppocire (Gattefossé), colloidal silicon dioxide (Aerosil) (Degussa), ethanol and glycerol (Chimopar), methylparaben, propylparaben (Merck) were used.

### Fluidextract preparation

The 1:1 fluid extract was obtained using Squibb repercolation technique [3]. Plant material, 1000 g, was mixed with a small quantity of extractive liquid (70% ethylic alcohol) and then left 30 min for a complete impregnation. Various amounts (500 g, 300 g and 200 g) were then introduced in three percolators. The solvent was introduced in the first percolator (containing 500 g vegetal product) and 200 g fluidextract was collected and then another three of 500 g fluidextract were collected. It was followed the extraction of the 300 g fraction of the vegetal product from the second percolator using sequentially all three secondary percolates, collecting 300 g fluidextract and another three of 200 g fluidextract. The third 500 g fraction was collected

from the third percolator using the three 200 g secondary percolates from the previous percolation. All the three collected fractions (200g, 300g and 500g) of fluidextract summarized 1000 g, the same mass like of the used vegetal product.

### Dosage forms formulation and preparation

The composition of the topical formulations is presented in Table I.

**Table I.** Composition of formulations based on *Ruscus aculeatus* fluidextract.

Gel	Hydrophilic cream	Suppositories
Fluidextract 10 g	Fluidextract 10 g	Fluidextract 10 g Aerosil** 1 g Suppocire ad 100 g
Carbopol 940 1 g	Cethylic alcohol 12 g	
TEA 1 g	Sodium lauryl sulfate 1 g	
Preservative* 1 g	Glycerol 15 g	
Water ad 100 g	Preservative* 1 g	
	Water ad 100 g	

\* 10 % alcoholic solution of methyl and propylparaben 3:1

\*\* colloidal silicon dioxide

Gel preparation consisted in the swelling of Carbopol with the fluidextract and the alcoholic solution (10%) of methyl and propylparaben. 80% of the total water heated at 50°C was added to swollen Carbopol, under gentle stirring. The dispersion was allowed to stand at hydration for 3 hours. A TEA solution prepared in the remaining 20% water was added for neutralization. The final mass was adjusted at initial with water [4,5].

For cream preparation, all the components were heated and the mixture homogenized to obtain a milky emulsion. After completing the mass with water, the emulsion was cooled under gentle and continuous stirring [6].

The suppositories were prepared by fusion and melt-molding method. The fluidextract adsorbed on Aerosil particles was dispersed in the melted suppository base. The homogenized fluid mixture was poured into a suppository mold, cooled and the finished suppositories removed by opening the mold [7].

### Characterization of dosage forms

In order to evaluate the physical stability, all formulations were tested as a fresh preparation and after one year storage at cool (8-15°C). All the tests (except, disintegration of suppositories) were done at 25°C. The semisolid preparations were tested for homogeneity, spreading capacity, consistency and rheological properties, while the suppositories were tested for homogeneity, resistance to rupture and disintegration.

**Homogeneity:** This test, mentioned in Romanian Pharmacopoeia X<sup>th</sup> ed., is intended to identify drops

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or particle agglomerations in semisolid preparations and particle agglomerations, crystals or air bubbles in suppositories. About 250 mg semisolid preparation were transferred on a microscope slide and spread in a thin layer. The suppositories were longitudinally sectioned. All samples were examined with a magnifying eyeglass (4.5 x) [8].

**Spreading capacity:** This test measures the semisolid preparation capacity of spreading between two glass plates. The sample (1 g) was placed between two horizontally glass plates and at 1 min intervals, was pressed with 100 g progressively cumulated weights. The circle radius formed by the sample was measured. The determination was stopped when three successive radius values remained unchanged. The test was made in triplicate and results are presented graphically, plotting the surface of circle ( $\text{mm}^2$ ) vs. cumulative weight (g) [7].

**Consistency** was evaluated by measuring the penetration of an object into the product in a container with a specified shape and size. This test is described in Romanian Pharmacopoeia, X<sup>th</sup> ed. 2001 Supplement [9] and we used a similar apparatus. This apparatus consists of a penetrometer and a cone penetrating object. Three containers were completely filled to obtain a flat surface, without forming air bubbles. The depth of cone penetration was measured every 10 seconds. The determination was stopped when three successive measurements remained unchanged. The penetration is expressed in millimeters as the arithmetic mean of three measurements [7].

**Rheological properties** were performed with the rotating viscosimeter Rheotest (Germany). The rheograms present the evolution of shear rate ( $\text{D: s}^{-1}$ ) and apparent viscosity function of shear stress ( $\text{T: dyn/cm}^2$ ) [7, 10].

**Resistance to rupture.** This test determines the resistance to rupture of suppositories measured by the mass needed to rupture them by crushing. The apparatus used was similar with the apparatus described in Romanian Pharmacopoeia X<sup>th</sup> ed. 2001 Supplement [9]. Sample crushing was carried out by successively adding of 200 g weights every 1 min. The mass required to crush the suppository was calculated by the sum of the masses weighing on the suppository when it collapsed, assessed as follows: if the suppository collapses within 20 s of placing the last weight, do not take this mass into account; if the suppository collapses between 20 s and 40 s of placing the last weight, use only half of this mass in the calculation (100 g); if the suppository remains uncrushed for more than 40 s after the last weight is placed, use all the mass in the calculation. The test was performed on ten suppositories for each category, at 25°C [7].

**Disintegration:** The test for disintegration of suppositories determines whether suppositories disintegrate within a prescribed period when placed in a liquid medium under the experimental conditions. The test was done in accord with the Romanian Pharmacopoeia X<sup>th</sup> ed. method

[8]. Disintegration end was considered when the molded suppository separated into its component parts that may collect on the surface, sink to the bottom or dissolve. Three suppositories from each category were tested. The disintegration time for lipophilic suppositories must be less than 30 min.

## RESULTS AND DISCUSSIONS

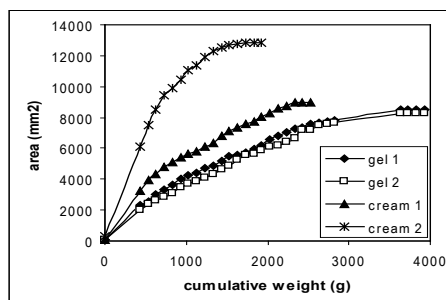
The gel formula contains the Carbopol (polyacrylic acid) a gelling agent very frequently used in the topical preparations. Because the gels are very easy contaminated by the microorganisms, the association of a preservative is important for the stability. The preparation technique is based on the swelling process of Carbopol and the neutralization with TEA. The gel obtained is homogeneous, clear, without drops or particles and yellow to light-brown colored.

The cream is an oil-in-water emulsion system. The cetyllic alcohol is the lipophilic excipient, emulsified by the sodium laurylsulfate in the external hydrophilic phase (hydrophilic cream). The fluidextract being miscible with water it is included in the external phase of the emulsion. The association of a preservative is also recommended. After preparation the cream is homogeneous, without drops, particles, oily or water phase separation, white to light-brown colored. Both, the gel and the cream are water-washables.

Suppocire, a semisynthetic glyceride, is frequently used as suppository excipient. In the first stage, the incorporation of the fluidextract in this lipophilic excipient was not possible because the two media are not miscible. The Aerosil preclude this inconvenient due to its propriety to adsorb the fluidextract, the mixture Aerosil-fluidextract being very easily homogenized in the molted Suppocire. The suppositories were very homogeneous, uniform, yellow-brown colored, without particles or air bubbles.

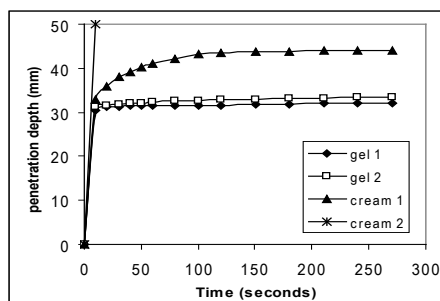
After one year storage, the gel remained homogeneous and free of drops or particles, yellow to light-brown colored. The cream examination showed an unhomogeneous sample, with a liquid phase separation. The suppositories preserved also their initial homogeneity.

Physical characterization of semisolid preparations might be done by the evaluation of some properties as spreading capacity, consistency or rheological behavior. The Romanian Pharmacopoeia X<sup>th</sup> ed. 2001 Supplement [9] recommends the measurement of consistency and viscosity but does not indicate specific values or results for these tests. However, all these tests are useful to study the influence of the formulation on semisolid preparations properties. Also, these tests offer the possibility to pursue the evolution in time of these physical properties and to evaluate thus the physical stability of the preparations.



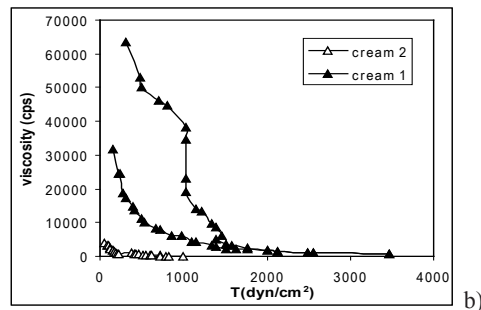
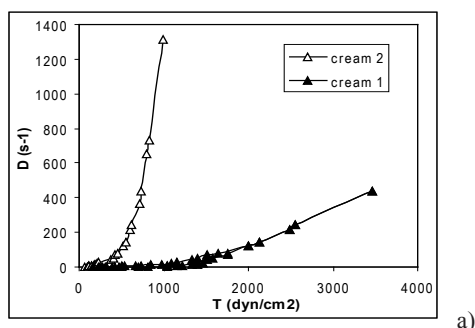
**Fig. 1.** Spreading capacity of gel and cream: gel 1 – fresh gel; gel 2 – one year stored gel; cream 1 – fresh cream; cream 2 – one year stored cream.

Figure 1 shows the spreading capacity of the gel and the cream. The two products tested immediately after preparation, had a similar behavior, the cream displaying a higher spreading capacity than the gel. After one year storage, the gel spreading capacity remained unchanged, while for the cream spreading capacity increased very much. This behavior can be explained by modifications of the cream matrix, by the loss of emulsion stability and liquid phase separation.



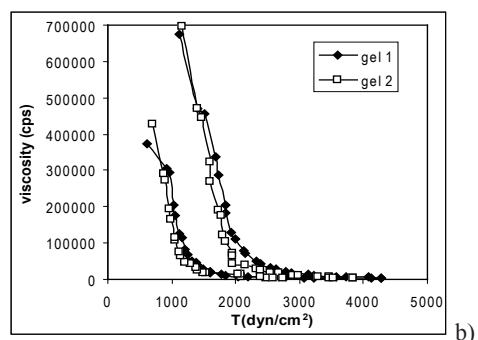
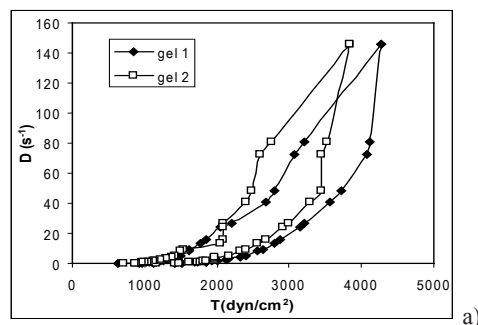
**Fig. 2.** Gel and cream consistency: gel 1 – fresh gel; gel 2 – one year stored gel; cream 1 – fresh cream; cream 2 – one year stored cream.

Cream consistency was lower than that of the gel in fresh preparations (the depth of penetration was higher for the cream). The gel maintained unchanged its consistency 1 year, while the cream consistency decreased very much within this period of time (the maximum penetration was obtained in only few seconds) (figure 2).



**Fig. 3.** Rheological behavior of cream: a) flow curves of cream (shear rate vs. shear stress); b) cream viscosity vs. shear stress (cream 1-fresh cream; cream 2-one year stored cream).

With regard to the rheological properties, the fresh cream exhibited a plastic flow, with a low yield value ( $317.2 \text{ dyn/cm}^2$ ) (figure 3a) and reduced thixotropy (final viscosity 31720 cps vs. 63440 cps initial viscosity) (figure 3b). One year stored cream shows a pseudoplastic (shear-thinning) flow (figure 3a), with a very low viscosity as compared with the fresh cream (initial viscosity of one year stored cream 3800 cps vs. 63440 cps initial viscosity for the fresh cream) (figure 3b). The modification of the flow properties of the cream, from plastic flow to pseudoplastic flow indicates that the internal structure of the cream suffered important changes. It is possible that the two immiscible phases changed their initial disposition.



**Fig. 4.** Rheological behavior of gel: a) flow curves of gel (shear rate vs. shear stress); b) gel viscosity vs. shear stress (gel 1 – fresh gel; gel 2 – one year stored gel).

The gel presented a plastic flow (yield value is  $1122.55 \text{ dyn/cm}^2$ ) (figure 4a), exhibiting a thixotropic

behavior, indicated by the hysteresis loop (figure 4a) and by the difference between the final viscosity (373584 cps) and the initial viscosity (676234 cps) (figure 4b), characteristics which remained unchanged within one year of storage (yield value 1153 dyn/cm<sup>2</sup>; final viscosity 425602 cps; initial viscosity 695150 cps) (figures 4a, 4b).

**Table II.** Results of suppositories testing.

Test	Suppositories 1*	Suppositories 2**
Resistance to rupture (kg) ± DS	2.65 ± 0.24	2.75 ± 0.20
Disintegration time (minutes)	9 – 11	14 – 16

\* after preparation

\*\* after one year stored

The results for suppositories (Table II) showed that the resistance to rupture was very similar for the two categories of suppositories. The disintegration time increased with a few minutes for the suppositories one year stored (14-16 min vs. 9-11 min), but the two categories of suppositories are in accord with Romanian Pharmacopoeia X<sup>th</sup> ed. requirements (disintegration time for suppositories with a fatty base is maximum 30 minutes) [8].

Physical stability of the pharmaceutical dosage forms is a very important characteristic for the medicines quality. It may influence the homogeneity of active compounds in preparations and the uniformity of content. The gel and the suppositories prepared and analyzed in this study are physically stables and their characterization may be continued with other *in vitro* pharmaceutical tests as drug content and drug release.

## CONCLUSIONS

We prepared three formulations containing 10%

*Ruscus aculeatus* fluidextract: gel, hydrophilic cream and suppositories. We demonstrated that the gel and the suppositories are stable regarding their physical properties (homogeneity, spreading capacity, consistency and viscosity) within one year stored (8-15°C). The hydrophilic cream suffered modifications at the level of emulsion stability with the loss of homogeneity, the decrease of consistency and viscosity and the increase of its spreading capacity. The hydrophilic cream formulation must be optimized in order to improve the emulsion stability.

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