DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(19), 2253-2259 (1995)

COMMUNICATIONS

FORMULATION OF PROPOLIS EXTRACT EMULSIONS. II. O/W CREAMS FORMULATED WITH SELF-EMULSIFYING BASES

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ABSTRACT

Propolis extract O/W emulsions, formulated with self-emulsifying bases are prepared. Type and optimal concentration of excipients (bases, consistency agents, solubilising factors) are chosen to obtain stable emulsions with desirable macroscopic properties, satisfactory consistency compatible with cutaneous application, in wound healing.

INTRODUCTION

We recently undertook the development of dosage forms of standardised propolis extract (1), rich in flavonoids and phenolic acids (2), which confer useful wound healing properties (3,4). Hydrophobic and hydrophilic ointments were prepared (5), together with O/W emulsions based on non-ionic surfactants and various consistency agents (6).

The work described here concerns the development of O/W creams suitable for the treatment of bed sores at various stages, formulated from self-emulsifying bases. During skin regrowth, the improvement of tissue elasticity and prevention of cheloids are essential. For this purpose, it is desirable to use semi-fluid creams that spread easily and have marked hydrating properties. These preparations are also suitable for preventive trophic massages.

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However, at the scar budding stage, it is preferable to apply compresses impregnated with creams, which therefore should have a semi-stiff consistency. The formulations of these emulsions was followed up by physical stability testing.

MATERIAL AND METHODS

Raw Materials

Active ingredient

Propolis extract was prepared by extraction with a Soxlhet extractor, using 70% (v/v) ethanol (1). The extractive solution was concentrated under reduced pressure at 40°C to stiff consistency (dry extract 80%).

Excipients

We used a thick paraffin oil associated with a moistening additive, glycerol (Coopération Pharmaceutique Française), a solubilising agent, Cetiol HE® (Henkel) and a cutaneous penetration factor isopropyl palmitate (Unichema).

The following self-emulsifying bases were tested : Tegin P® (Goldschmidt), Hostacerin CG® (Hoechst) and Emulgade 1000 NI® (Sidobre Sinnova) associated with a consistency agent, Cutina MD® (Sidobre Sinnova).

Methods

Preparation of the Emulsions

The dispersion of water in the lipophilic phase was performed at 70°C with an IKA RW20 helical stirrer, as described previously (6).

Essays after fabrication

The following tests were performed 24 hours after preparation :

Macroscopic stability

The distribution of propolis extract and the homogeneity of the emulsions (no creamage or sedimentation) were checked by visual inspection (7).

Determination of Spreadability

One gram of emulsion was pressed between two horizontal plates 20 cm square, the upper one of which weighed 125 g, and its diameter (∅) was measured after one min.

Under the experimental conditions, the following classification was adopted : semi-stiff creams $\varnothing \leq 50$ mm and semi-fluid creams $50 < \varnothing \leq 70$ mm (7).

Penetrating Power

Penetrating power (P) was measured using a Prolabo penetrometer fitted with the penetration cone for lubricating grease (cone weight 47.5 g). The cone fall was automatically controlled timed at 5 seconds. Under these conditions, two types of creams can be distinguished : semi-stiff creams $P \leq 300 \pm 5$ 1/10 mm and semi-fluid creams $P > 300 \pm 5$ 1/10 mm.

Rheological Study

The rheological study of the emulsions was carried out at 21°C using a Brookfield RVTD V2 instrument fitted with an SC4-28/13R small adapter.

pH Determination

We used a CG 837 Schott pHmeter (7).

Stability Tests

The emulsions were packed in opaque tubes and stored at room temperature (23 ± 2 °C) (7). For each formulation, the parameters previously described were checked at regular time intervals (3, 6 and 12 months) : macroscopic stability, spreading diameter, penetrating power, rheological study and pH determination.

RESULTS AND DISCUSSION

Formulation

The active substance is concentrated propolis extract, used at its optimally effective concentration of 5% w/w (4). As previously (6), thick paraffin oil (5% w/w) was associated with a moisturising agent, glycerol (5% w/w), which improves skin elasticity (9). We also used a skin penetration factor, isopropyl palmitate (6% w/w), which confers an excellent spreadability and a high degree of creaminess (10).

Dissolution of the propolis extract in the paraffin oil-glycerol-isopropyl palmitate mixture was achieved using a mixture of esters of polyoxyethylenated fatty acids of coconut, Cetiol HE®, which possesses softening properties. This excipient was initially incorporated at a concentration of 8% w/w, as in emulsions developed previously (6).

We tested three non-ionic self-emulsifying bases, Tegin P®, Emulgade 1000 NI® and Hostacerin CG®, which theoretically obviate adding surfactants and confer marked hydrating properties on the emulsion (11). The compositions of the different formulations made up and their test results are summarised in table 1.

Emulgade 1000 NI®, a colloid dispersion of cetostearyl alcohol and non-ionic emulsifiers based on polyglycol ethers of saturated fatty alcohols, is a self-emulsifying base that also possesses a high dissolving power (12). It is designed to be used at a concentration of 2% w/w and requires an additional consistency factor. We chose Cutina MD® (12% w/w), often prescribed in formulation guides (13) and which had already given excellent results (6). The emulsion thereby obtained, of semi-stiff consistency and rheologically pseudoplastic-thixotropic, displayed excellent macroscopic characteristics (formulation 1) and so was selected for physical stability testing.

Other self-emulsifying bases, e.g. Tegin P® and Hostacerin CG® offer the advantage of overcoming emulsion consistency problems.

Tegin P®, propylene glycol monostearate, is usually used at concentrations of 4 to 8% w/w to emulsify 15 to 30% w/w of lipid phase (14). Its surfactant power proved insufficient here, even at higher doses (formulations 2 and 3). As shown in table 1, coalescence persists.

TABLE 1
O/W Emulsions formulated with self-emulsifying Bases

Formulation N°	1	2	3	4	5	6	7	8	9	10
Raw materials % (w/w) (demineralised water to 100%)										
Propolis extract	5	5	5	5	5	5	5	5	5	5
Thick paraffin oil	5	5	5	5	5	5	5	5	5	5
Glycerol	5	5	5	5	5	5	5	5	5	5
Isopropyl palmitate	6	6	6	6	6	6	6	6	6	6
Cetiol HE®	8	8	8	8	8	8	8	10	10	10
Emulgade 1000 NI®	2			2			2	2	2	2
Tegin P®		8	12	8						
Hostacerin CG®					12	15	15	15	12	10
Cutina MD®	12									
Homogeneity	+						-	+	+	+
Coalescence	-	+	+	+	+	±	-	-	-	-
Creamage	-						-	-	-	-
Sedimentation	-						-	-	-	-
∅ after 1 min (mm)	50	-	-	-	-	-	-	?*	50	59
P (1/10 mm)	299	-	-	-	-	-	-	-	292	359
η at 5 r.p.m. (m.Pa.s. x 10^3)	158	-	-	-	-	-	-	-	38	109
pH	6.4	-	-	-	-	-	-	-	6.1	6.1

* ∅ not measurable

Hostacerin CG®, a mixture of ethoxylated alkanolamides of oleic acid, ethoxylated esters of phosphoric acid and secondary alkanesulphonates with aliphatic alcohols, is recommanded at concentrations ranging from 5 to 15% w/w (15).

Emulsification of formulation 5, containing 12% w/w of Hostacerin CG® proved impossible ; formulation 6 prepared with 15% w/w of this agent displayed partial coalescence.

As previously, we associated this self-emulsifying base with Emulgade 1000 NI®. Formulation 7 thus afforded a macroscopically stable cream, but with a stiff consistency and heterogeneity arising from incomplete solubilisation of propolis extract in the lipophilic phase. In contrast, the cream containing 15% w/w of

TABLE 2
Physical Stability of O/W Emulsions
Spreading Diameter, penetrating Power and Viscosity

Formulation N°		A	B	1	9	10
∅ after 1 min (mm)	3 months	55	50	50	50	60
	6 months	55	50	50	51	61
	12 months	56	51	50.5	53	64
P (1/10 mm)	3 months	318	298	297	292	359
	6 months	318	299	298	293	361
	12 months	318	302	301	295	365
η at 5 r.p.m. ($m.Pa.s. \times 10^3$)	3 months	14	143	144	37.5	107
	6 months	13.5	139	140	35.2	101
	12 months	12.5	134	134	32	90.8

Hostacerin CG® and 10% Cetiol HE® was homogeneous but was too stiff to be spread on the skin (formulation 8). Lowering the percentage of Hostacerin CG® afforded satisfactory preparations. Thus formulation 9 made up with 12% w/w of this base was of the semi-stiff type, while formulation 10, which contains 10% w/w, was semi-fluid. These two emulsions, chosen for physical stability testing, were rheologically pseudoplastic-thixotropic.

Physical stability tests

Only three creams were subjected to stability testing, namely formulations 1, 9 and 10. The first two, of semi-stiff consistency, are suited to curative treatment of bed sores at the budding stage. Formulation 10, which is semi-fluid, is preferable during skin reforming and preventive massaging.

Tests of physical stability in the dark at room temperature were carried out at regular time intervals (3 months, 6 months and one year) to monitor the following parameters : macroscopic stability, pH, viscosity (7), spreadability and penetrability (6).

After one year's storage in the dark at room temperature, all the creams displayed perfect macroscopic stability and their pH was unchanged.

The stability of the other parameters is summarised in table 2. This table also reports the results obtained with the most stable emulsions prepared associating non-ionic ester surfactants and consistency factors (formulations A and B) (6).

Formulation A contains 5% cetyl alcohol as consistency agent and 1.5% Eumulgin B1® and Eumulgin B2® as surfactants. Formulation B contains 12% Cutina MD® likewise associated with the Eumulgin B1-B2® pair, at the same concentrations. Both creams are semi-stiff.

The creams made up with the Emulgade 1000 NI®/Hostacerin CG® self-emulsifying bases showed a marked tendency to fluidise over time (formulations 9 and 10).

In contrast, the spreading diameter and penetrability of formulation 1, combining Emulgade 1000 NI® and Cutina MD® were hardly modified, and viscosity loss was only 9% in one year. This emulsion had a stability comparable to or better than those of formulations A and B. It is of particular interest in that it combins the marked hydrating ability of the self-emulsifying base with the stabilising power of the consistency agent. This semi-stiff cream is suitable for the impregnation of compresses used during bed sore healing, especially at the budding stage. Further work to verify the stability of these emulsions is currently in progress.

ACKNOWLEDGEMENTS

The authors wish to acknowledge P. LEGRET for his technical assistance.

REFERENCES

1. A. ARVOUET-GRAND, B. VENNAT, A. POURRAT, P. LEGRET, Standardisation d'un extrait de propolis et identification des principaux constituants, *J. Pharm. Belg.*, n° acceptation 409 (1994).

2. B. VENNAT, A. ARVOUET-GRAND, A. POURRAT, Propolis extract: Quantitative analysis of flavonoids and identification of phenolic acids, *J. Pharm. Belg.*, sous presse.

3. A. ARVOUET-GRAND, B. LEJEUNE, P. BASTIDE, A. POURRAT, Extrait de propolis, I- Etude de la toxicité aigüe et détermination de l'indice d'irritation primaire cutanée, *J. Pharm. Belg.*, **48**, 3, 165 (1993).

4. A. ARVOUET-GRAND, B. LEJEUNE, P. BASTIDE, A. POURRAT, Extrait de propolis, II- Etude de la cicatrisation de plaies chez le Lapin et chez le Rat, *J. Pharm. Belg.*, **48**, 3, 171 (1993).

5. A. ARVOUET-GRAND, B. LEJEUNE, A. POURRAT, Formulation de pommades à base d'extrait de propolis, *Lyon Pharm.*, in press.

6. A. ARVOUET-GRAND, B. VENNAT, B. LEJEUNE, A. POURRAT, Formulation of propolis extract emulsions Part I : O/W creams based on non-ionic surfactants and various consistency agents, *Drud Dev. Ind. Pharm.*, **21**, 16, 1907 (1995).

7. PHARMACOPEE FRANCAISE , IX et X édition, Maisonneuve éditeur, Paris.

8. B. VENNAT, D. GROSS, A. POURRAT, Formulation of hydrogels.Choice of the excipients and validation of an original control method:determination of the spreading diameter, *13th Pharmaceutical Technology Conference,* Strasbourg, France, April 12-13-14th (1994).

9. M.C. MARTINI, M. SEILLER, Actifs et additifs en cosmétologie, Lavoisier édition, Paris (1992).

10. UNICHEMA, *Tech. Doc.* Isopropyl palmitate.

11. M.C. MARTINI, L. PLANCHETTE, B. GLAS, L. WAGINAIRE, Influence de la base lipidique d'une émulsion sur l'hydratation cutanée, *Parfums Cosmétiques et Arômes,* **58**, 59 (1984).

12. SIDOBRE-SINNOVA, *Tech. Doc.*, Emulgade 1000 NI® and Cutina MD®.

13. PENTAPHARM LDT, Guide formulation, *Tech. Doc.,* Basle (1990).

14. GOLDSCHMIDT AG, *Tech. Doc.,* Tegin P®

15. HOECHST, *Tech. Doc.,* Hostacerin CG®