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FEASIBILITY STUDY OF DERMATOLOGICAL FORMULATIONS BASED ON SHEABUTTER FOR THE TROPICAL COUNTRIES OF AFRICA

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ABSTRACT

Sheabutter is an abundant raw material in certain West African countries, but its low melting point for a tropical climate and the variability of its chemical composition, due to its extraction method, limit its use.

However this work has permitted to realize lipophile bases from sheabutter, with satisfactory pharmacotechnical characteristics (melting point, consistence, heat stability) according to the following procedure:

_ Comparison of Burkina Faso sheabutter(BB) physicochemical properties with those of a purified sheabutter, Cetiol SB 45* (CT).

_ Formulation and control of lipophilic ointments

_ Evaluation of griseofulvin availability, widely used in Burkina Faso, from different formulations.

The appropriate choice of auxiliary substances has allowed to obtain a dermatological formulation having a suitable consistence, a proper heat stability and a satisfactory activity release in comparison with reference formulation.

INTRODUCTION

In Western Africa, almost pharmaceutical products are imported resulting in:

_ Products that are not adapted to local use

_ Lack of efficiency due to the conditions of storage and distribution

_ Lack of effective medications for pathologies encountered

Burkina Faso produces oleaginous raw materials which can be used to realize topical dosage forms. However their chemical properties do not permit their utilization directly.

It is particularly necessary to optimize appropriate vehicles obtained from local raw materials in order to adapt their fabrication and use to economic conditions (limited choice of raw materials, simple technology) and climatic ones (tropical climate)

The aims of these investigations were:

_ To study the physicochemical characteristics of Burkina Faso sheabutter (BB), widely used in West Africa, and to compare them with a purified sheabutter, Cetiol SB 45* (CT)

_ To formulate bases for topical drug forms having satisfactory pharmacotechnical properties (melting point, consistence, heat stability) from the both different sheabutters.

_ To evaluate the avaibility of an antifongic drug, widely used in Burkina Faso and incorporated to raw materials and to the best formulations.

.MATERIALS

* Sheabutters

BB is produced by a local factory (CITEC) and the CT is provided by Henkel (Germany).

* Beeswax (Cooper, France)

Beeswax has been employed to increase melting point of bases and selected because on its avaibility in Africa.

* White petrolatum, Sesame oil (Cooper, France)

The two components have been used to adjust the formulation consistence after addition of beeswax. Such as the above mentionned, there is no problem of supply. Morever sesame oil posseses a real resistance at oxydation (1).

* Griseofulvin (G.L. Champion, France).

Griseofulvin has been choosen in account of importance of dermatosis in West Africa. This drug has the appearance of a white micronized powder (5µm)

All these products are in accordance with the French Pharmacopeia (2), except sheabutters for which there is no monography.

METHODS

* Base and ointment manufacturing process

Auxiliary substance fusion has been realized using water bath at 70°C. Then, the mixture has been cooled to room temperature under constant stirring, using a rotatory dispersion device moving at 450 RPM (Grenier-Charvet, France). Concerning ointment preparation griseofulvin (5%) has been dispersed in the melted mixture (40°C). The homogeneisation has been obtained by stirring until cooling in the same conditions than previously.

* Evaluation tests

Determinations of sheabutter physicochemical characteristics.

_ Melting point.

This assay has been realized according to the opened capillary tube (2).

_ Physicochemical indexes.

The following indexes (acid, iodine, peroxyde, unsaponifiable) have been determined according to the French Pharmacopeia (2).

_ Differential scanning calorimetry (DSC) (General V2-2A Dupont 9000).

DSC has been realized with the both sheabutters and with the formulations B (sheabutter+beeswax) and Bs (sheabutter+beeswax+ sesame oil), in order to elucidate the behaviour of the different components at heat and to establish correlation between spreading and heat stability.

This procedure is described by Hampson (3) and was carried out using a sample of 6 mg, with heating rate (10°C/min) during a range of temperature from 0°C to 100°C.

This procedure consists in measuring energetic variations of a substance, submitted to increasing temperature, visualized by a thermogram. Structure differences polymorphism, vitreous fusions and transitions are observed with this device. (3,4.).

_ Extensometry

Consistence of the bases has been determined by extensometry, according to Amdidouche procedure (5).

This method consists in measuring the area taken by an ointment disk (diameter=20mm-thickness=6mm), under the pressure done by a glass plate undergoing an increasing mass for one minute at room temperature. The range of mass extends from 100 g to 400 g. The ointment is put on a glass plate (diameter=10 cm) graduated in four directions. It allows to calculate surface ($S=mm^2$) according to the following equation:

$$S = \frac{d^2 \cdot \pi}{4}$$

where d (mm) denotes the mean parameter diameter of four values observed on the gradient plate. Two assays have been realized with every sheabutter.

Tests concerning raw materials and final products.

_ Melting point, extensometry and DSC.

These experimentations have been realized according to procedures described previously.

_ Temperature stress test.

This test is important because of the climatic conditions of Africa. This control has been carried out at 35°C and at 50°C, considered as room and storage temperatures.

_ **In vitro** release tests.

Release tests were carried out with Guyot-Herman cells, according to the procedure described by Zuber (6).

One gram of raw material or ointment has been spread on a polydimethylsiloxane membrane (Silastic, thickness=0,130mm, Dow Corning, France), the whole being mounted on a cell immersed into 100ml of ethanol, solvent of active drug.

This receiving phase has been submitted to a constant magnetic stirring, at 30°C $\pm$1°C. Six samples have been taken at first, second and third hour. The liberated griseofulvin has been measured by an UV spectrophotometer assay at 291nm.

RESULTS and DISCUSSION.

* Sheabutters.

Melting point and physicochemical indexes.

The values of these assays are described in Table 1

The comparison of the results shows, concerning Burkina Faso sheabutter:

_ A weaker melting point, which needs an increasing of it in the formulations.

_ The important quantity of free fatty acids due to the difference of raw material treatment.

_ A higher peroxyde index, showing an alteration.

_ A less powerful content in unsaponifiable, having no consequences in formulation.

DSC.

The observation of thermograms (figures 1 and 2) has shown differences at the level of the enthalpy melting and thermodynamic potential peaks (31,13 J/g and 47,24 J/g_ 25,88°C and 19,71°C) for the CT and BB respectively.

These results reveal structure modifications between the two substances: the BB having a much more difficult structure to desorganize, but having a weaker melting temperature.

TABLE 1.

Comparison of the physico-chemical properties of the two sheabutters (n=5)
(BB= Burkina Faso sheabutter /CT= Cetiol SB 45*)

	BB	CT
Melting point(°C)	36,20	40,00
Acid index	25,13	0,05
Iodine index	62,94	70,00
Peroxyde index (mEq/Kg)	6	1,2
Unsaponifiable	6,6	10,3

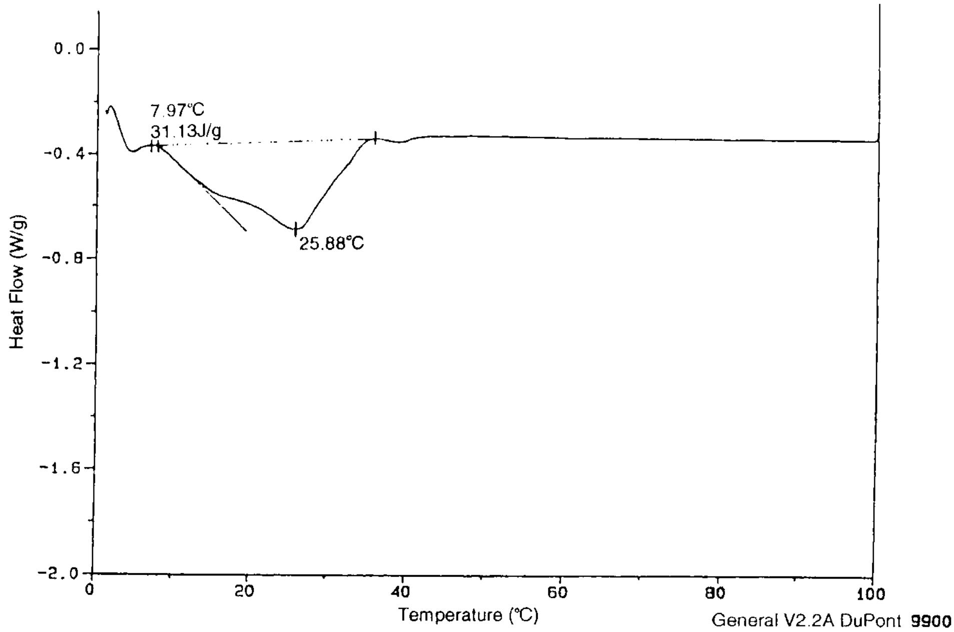

Figure1.- D.S.C. results of the Burkina-Faso sheabutter (BB)

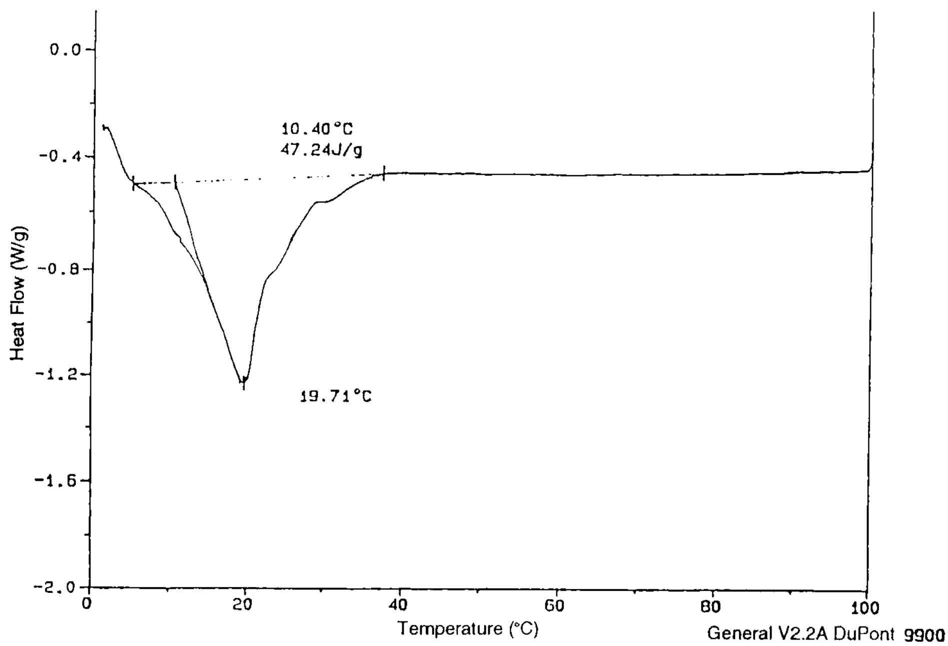

Figure2- D.S.C. results of the Cetiol SB 45* (CT)

Extensometry.

The measured consistence by extensometry at room temperature has not shown any important difference between the two components (figure 3). The results of weaker spreading obtained with Cetiol* can be explained by a higher melting point.

Heat stability.

No difference has been described between the two products.

Release experimentation.

The tests were carried out on all the raw materials except sesame oil, which should have gone through the lipophile membrane (figure 4). The CT has allowed to obtain release rate slightly superior to those obtained with BB, but the difference is not highly significant. On the other hand, the release quantities by white petrolatum or beeswax were very low.

* Bases.

The study of physicochemical and pharmacotechnic characteristic comparaison between the two butters has shown that BB could used as the main vehicle in the formulations of bases for ointments.

So the following mixtures have been done and submitted to most controls realized on sheabutters.

Three types of bases have been studied, all containing BB associated to beeswax (15-20-25-30-35%), to increase the melting point. They differed one to another, by the lack (ref. B) or the presence of either 10% of sesame oil (ref.Bs) or by 10% of white petrolatum (ref. Bv), in order to improve the consistence

Melting point.

The results (figure 5) have shown a melting point increase related to the beeswax percentage. On the other hand, the addition of sesame oil or white petrolatum has little influence on that parameter.

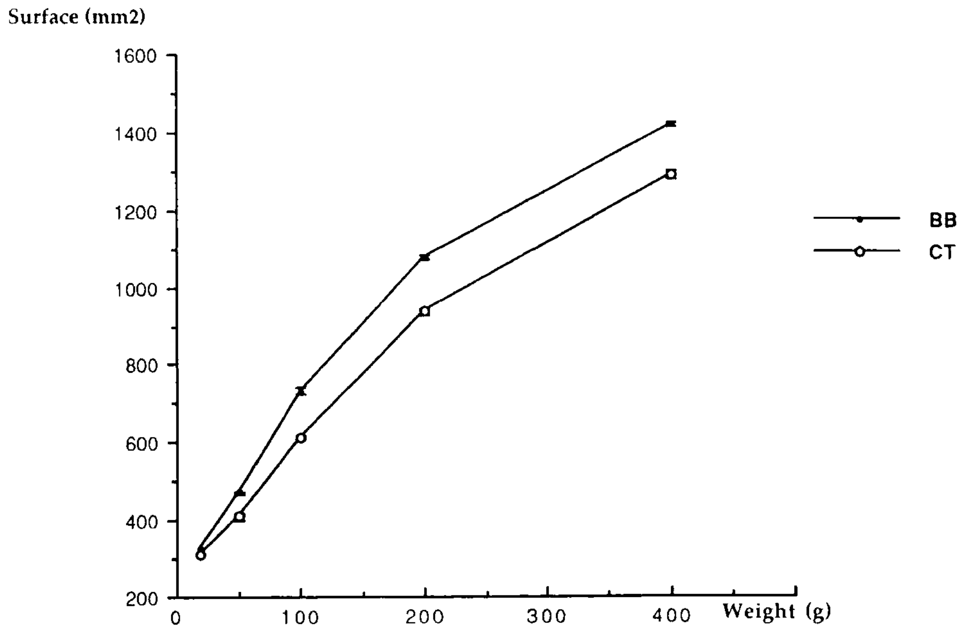

Figure 3.- Comparison of the sheabutter extensometry (n=2)

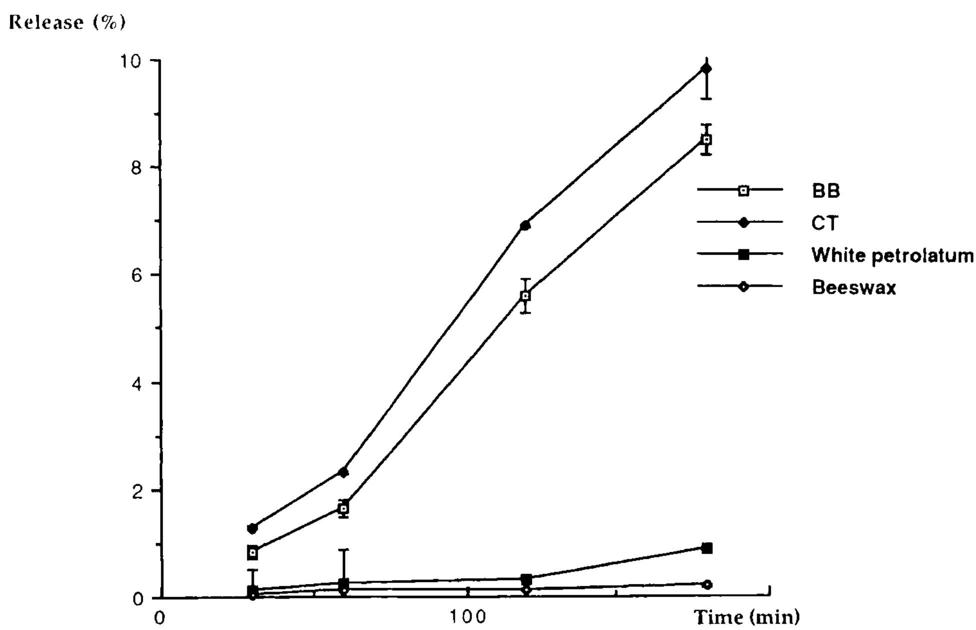

Figure 4.- Comparison of griseofulvin release from different raw materials (n=6)

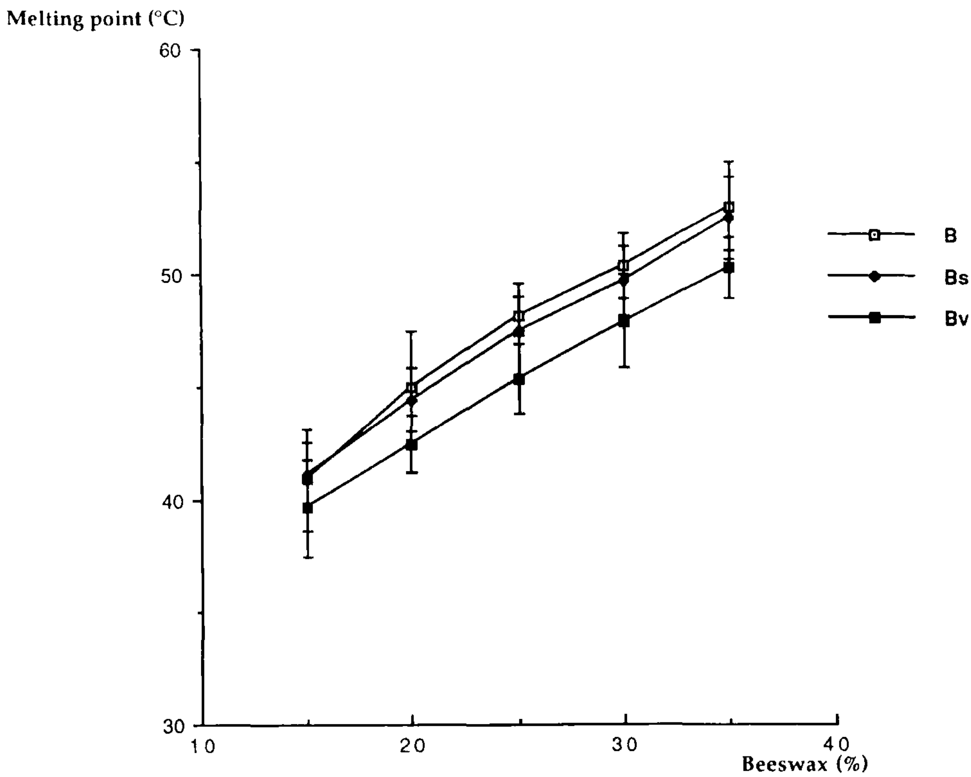

Figure 5.- Relationship between the beeswax percentage and the melting point of the different bases

DSC.

DSC shows that melting enthalpy decreases when the beeswax percentage increases, in spite of a high melting enthalpy of beeswax.(Table II)

Moreover, formulations containing sesame oil have weaker melting enthalpies. The beeswax increase and sesame oil addition would result in a modificated structure that is instable in heat.

The observation of thermograms (figures 6,7,8,9) shows the existence of two distinct peaks as if several structures coexisted, including two that are completely distinct. Following

TABLE 2

DSC results of the bases (B=Sheabutter+beeswax Bs=Sheabutter +beeswax+sesame oil/BB=Burkina Faso sheabutter)

Formulation with beeswax percentage	Melting point (° C)	Melting enthalpy (J/g)
B 15	31,19	84,69
B 30	32,35	45,90
Bs 15	34,94	35,95
Bs 30	49,33	15,96
Beeswax	34,41	147,90
BB	19,71	47,24

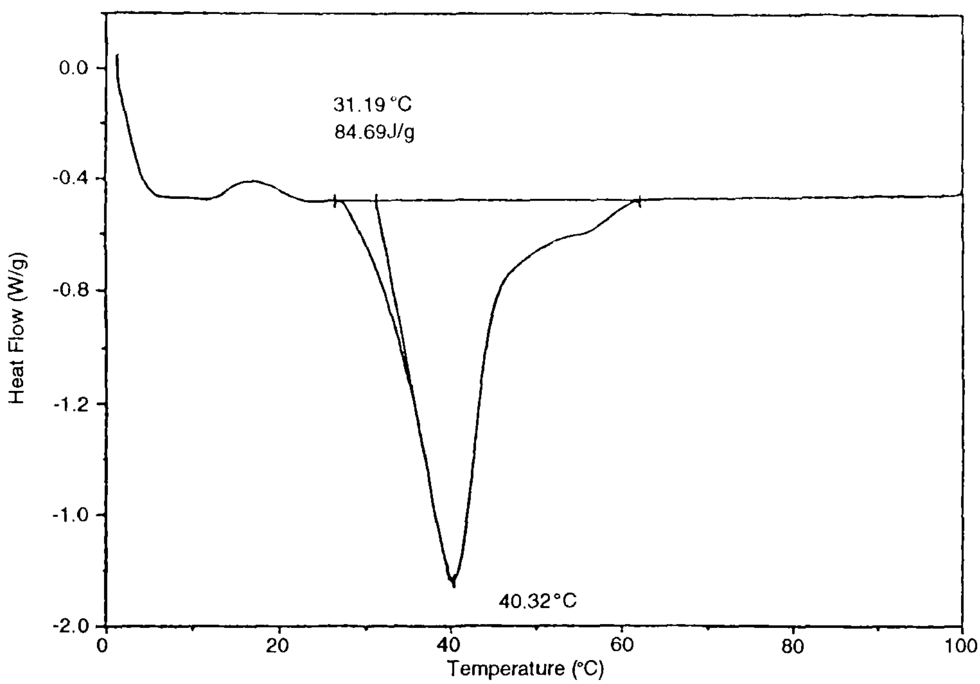

FIGURE 6. THERMOGRAM OF THE BASE B 15

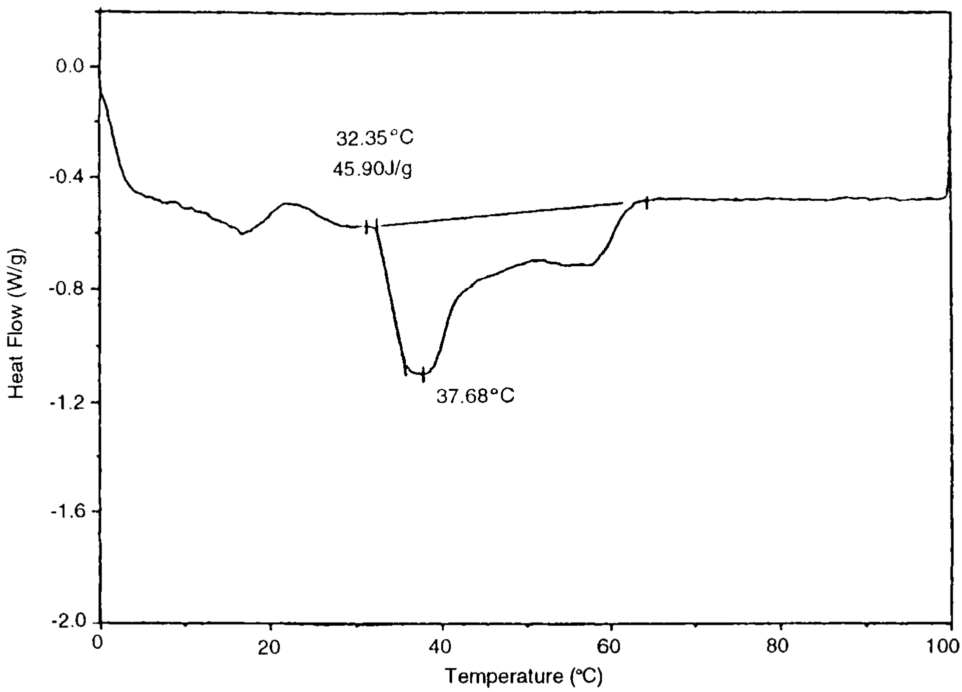

FIGURE 7 THERMOGRAM OF THE BASE B 30

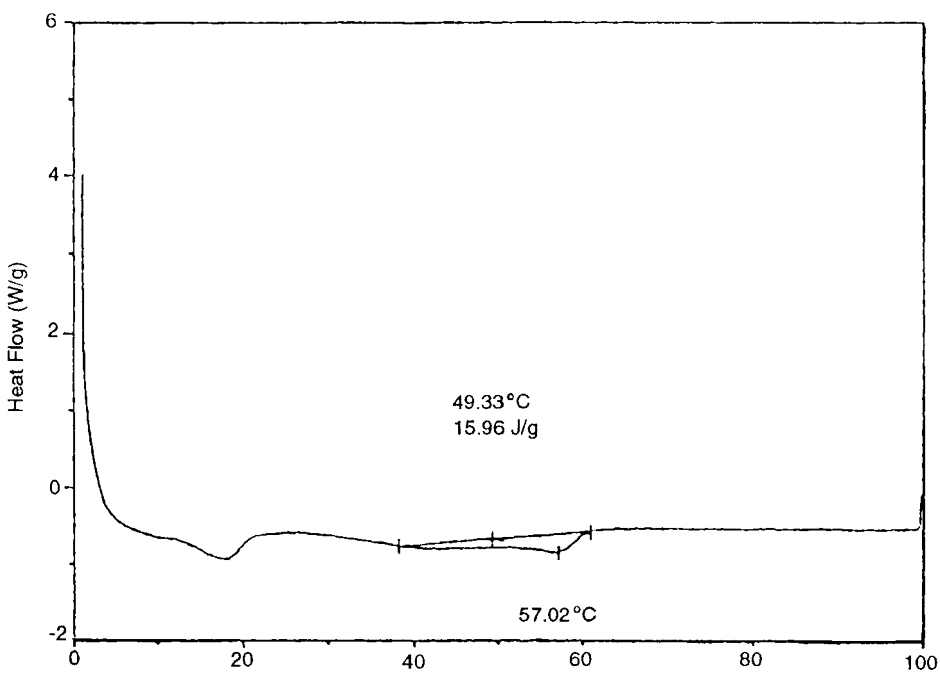

FIGURE 8 THERMOGRAM OF THE BASE BS 15

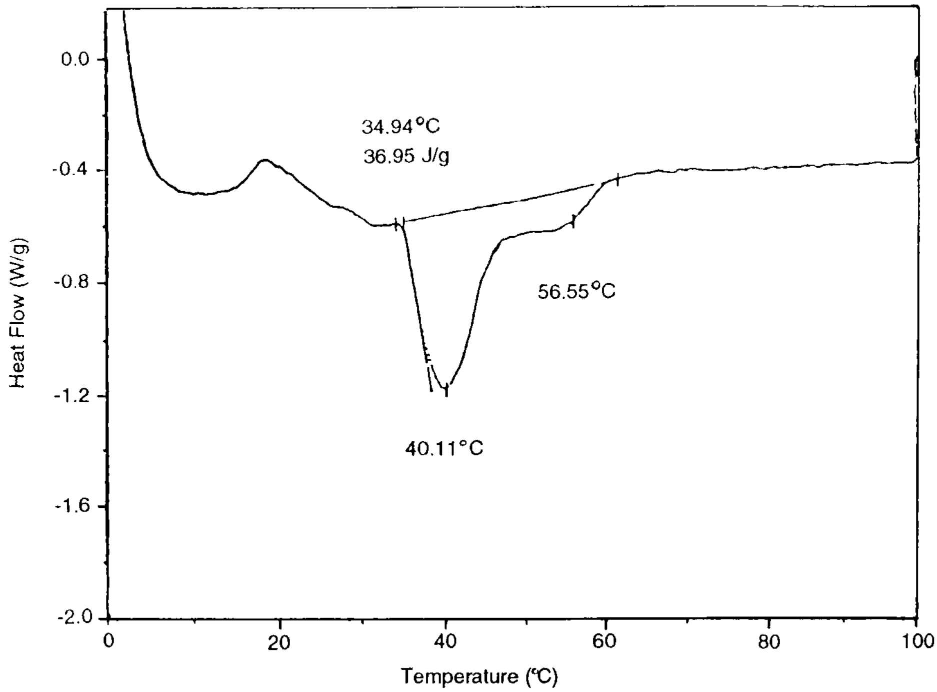

FIGURE 9 THERMOGRAM OF THE BASE BS 30

this hypothesis the homogeneity observed becomes apparent: the formulations therefore tend to alter on a more or less long time basis due to effect of the temperature.

Extensometry.

The results (Table 3) show that consistence increases with the beeswax percentage but decreases with sesame oil and above all white petrolatum. The addition of those two substances can facilite the spreading.

Heat stability.

At 35°C, all the bases were stable. At 50°C the only preparations containing 30% and 35% of beeswax were relatively stable In fact, a slight exsudat appeared after three month conservation.

TABLE 3

Extensometry results of bases, determined at 400 g, according to the beeswax concentration. (n=2)

Base	Beeswax (%)	Extensometry (mm^2)
B	15	1.017
	30	730
Bs	15	1.384
	30	934
Bv	15	2.787
	30	1.667

B=BB+beeswax
Bs=BB+beeswax+sesame oil (10%)
Bv=BB+beeswax+white petrolatum (10%)

Release assays

The experimentations have been realized with the ointments made with white petrolatum (10%), containing 30% or 35% of beeswax (stable to temperature) (figure 10). Grisefuline* (Clin-Midy), of the same concentration, has been choosen as a reference. The best results were obtained with formulations containing the most important concentration in BB, confirm those obtained previously. White petrolatum and beeswax have decreased the active drug release. But the release quantities by the selected formulations have been always superior with those obtained with Grisefuline*.

CONCLUSION

The aim of this study was to formulate dermatological prepararations, based on Burkina Faso sheabutter as main

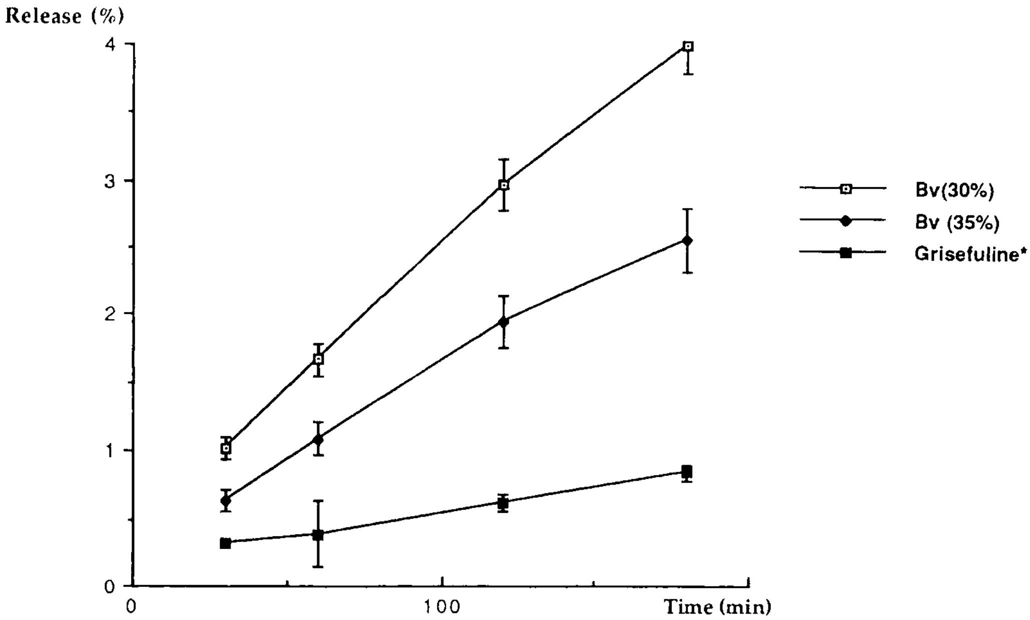

Figure 10._ Comparison of griseofulvin release from different formulations (n=6)

constituant. A lot of this raw material is found in West Africa, and particulate in Burkina Faso. But it was necessary to be sure that there physicochemical properties were adapted to the specified use.

At first, we are going to compare the characteristics of this raw material to a purified sheabutter (Cetiol SB 45*). Differences were revealed, in particular a too weak melting point, in order to be used in tropical climate, and index values showing problems of Burkina Faso sheabutter treament and alteration.

On the second hand, in spite of those results, we have set up formulations of lipophilic vehicles, based on sheabutter and beeswax, used at different concentrations, in order to increase the melting point.

The tests (melting point, consistence) have shown a real melting point increase, related with the proportion of beeswax, but provocating a bad spreading, improved by the addition of sesame oil and above all of white petrolatum.

In vitro release assays have completed that investigations. Griseofulvin has been choosen as an active drug, in account of the dermatomycosis importance in West Africa. It has been incorporated to the concentration of 5% in the raw materials and in the two formulations having presented a satisfactory stability at 50°C. The most important release quantities have been obtained with sheabutters, but without difference between them. On the other hand, beeswax and white petrolatum have showed down the active drug release.

The results obtained by the two formulations were correlated with those of raw materials. The ointment containing the highest percentage of sheabutter has been responsable of the highest release rate.

This study is interesting because it has showed that it was possible to realize dermatological formulations with raw materials and inexpensive devices.

However, it is necessary to establish a balance between the percentage of various vehicles to conciliate the pharmacotechnical characteristics and the disposition of griseofulvin.

Finally, the standardization of the raw material should be recommanded to certify the reproductibility of sheabutter physicochemical characteristics and a better stability of final product.

REFERENCES

1) TOSHIHIKO O., MASAYASU N., MITSUO N.,YASUKO F. Sesamolinol, a novel antioxydant isolated from sesame seeds. Agric. Biol. Chem., 1985,49,11,3351-3352.

2) PHARMACOPEE FRANCAISE X^{ème} EDITION Ed.Maisonneuve S.A Moulin-les-Metz

3) HAMPSON J. W. , ROTHBART H.L.
Triglycerids specific heat determined by the differential scanning calorimetry.
J. Amer. Oil. Chem. Soc. , 60, 6, 1102-1100, 1983.

4) YELLA S., PRABHAKAR H.
Study of the polymorphism of normal triglycerides of Sal (Shorea Robusta) fat by D.S.C. Effects of diglycerides.
J.Amer. Oil. Chem. Soc., 63, 5, 672-676, 1986.

5) AMDIDOUCHE D., DUTERTRE H., CHAUMEIL J.C.
Excipients composés pour pommades ophtalmiques destinées aux pays à climat tropical.
Pharm. Acta. Helv. 64, n°9, 10, 1989..

6) ZUBER M., CHEMTOB C.
Disponibilité à partir des formes dermiques. V. Etude de gels à l'aide de membranes poreuses et non poreuse et de phases réceptrices différentes.
Sci. Tech. Pharm.,1981,10, n° 5, 39-44..